This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

2 AM

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 April 2002 (04.04.2002)

PCT

(10) International Publication Number
WO 02/26723 A1

(51) International Patent Classification[7]: C07D 265/30, 267/10, A61K 31/5375, 31/553, A61P 11/06, C07D 413/06, 413/12, 417/12, 471/04, 413/14

(21) International Application Number: PCT/GB01/04350

(22) International Filing Date:
28 September 2001 (28.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0023973.1	29 September 2000 (29.09.2000)	GB
0107643.9	27 March 2001 (27.03.2001)	GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB06 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ANCLIFF, Rachael, Anne** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **COOK, Caroline, Mary** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **ELDRED, Colin, David** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **GORE, Paul, Martin** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HARRISON, Lee, Andrew** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HODGSON, Simon, Teanby** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **JUDD, Duncan, Bruce** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **KEELING, Suzanne, Elaine** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **LEWELL, Xiao, Qing** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **ROBERTSON, Graeme, Michael** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **SWANSON, Stephen** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: **GIDDINGS, Peter, John**; GlaxoSmithKline, Corporate Intellectual Property (CN9.25.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

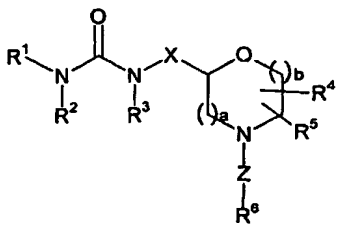
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/26723 A1

(54) Title: COMPOUNDS USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASES



(I)

(57) Abstract: There are provided according to the invention, novel compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, X a, b, and Z are as defined in the specification, processes for preparing them, formulations containing them and their use in therapy for the treatment of inflammatory diseases.

Compounds useful in th treatment f inflammatory diseases

This invention relates to novel chemical compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction. There is increasing evidence that the bronchial inflammation which is characteristic of asthma represents a specialised form of cell-mediated immunity, in which cytokine products, such as IL-4 and IL-5 released by Th2 T lymphocytes, orchestrate the accumulation and activation of granulocytes, in particular eosinophils and to a lesser extent basophils. Through the release of cytotoxic basic proteins, pro-inflammatory mediators and oxygen radicals, eosinophils generate mucosal damage and initiate mechanisms that underlie bronchial hyperreactivity. Therefore, blocking the recruitment and activation of Th2 cells and eosinophils is likely to have anti-inflammatory properties in asthma. In addition, eosinophils have been implicated in other disease types such as rhinitis, eczema, irritable bowel syndrome and parasitic infections.

Chemokines are a large family of small proteins which are involved in trafficking and recruitment of leukocytes (for review see Luster, New Eng. J. Med., **338**, 436-445 (1998)). They are released by a wide variety of cells and act to attract and activate various cell types, including eosinophils, basophils, neutrophils, macrophages, T and B lymphocytes. There are two major families of chemokines, CXC- (α) and CC- (β) chemokines, classified according to the spacing of two conserved cysteine residues near to the amino terminus of

the chemokine proteins. Chemokines bind to specific cell surface receptors belonging to th family of G-protein-coupled seven transmembrane-domain proteins (for review see Luster, 1998). Activation of chemokine receptors results in, amongst other responses, an increase in intracellular calcium, changes in cell shape, increased expression of cellular adhesion molecules, degranulation and promotion of cell migration (chemotaxis).

To date, 9 members of CC chemokine receptors have been identified (CCR-1 to 9). Of particular importance to the current invention is the CC-chemokine receptor-3 (CCR-3), which is predominantly expressed on eosinophils, and also on basophils, mast cells and Th2 cells (Luster, 1998). Chemokines that act at CCR-3, such as RANTES, MCP-3 and MCP-4, are known to recruit and activate eosinophils. Of particular interest are eotaxin and eotaxin-2, which specifically bind to CCR-3. The localization and function of CCR-3 chemokines indicate that they play a central role in the development of allergic diseases such as asthma. Thus, CCR-3 is specifically expressed on all the major cell types involved in inflammatory allergic responses. Chemokines that act at CCR-3 are generated in response to inflammatory stimuli and act to recruit these cell types to sites of inflammation, where they cause their activation (e.g. Griffiths et al., J. Exp. Med., **179**, 881-887 (1994), Lloyd et al., J. Exp. Med., **191**, 265-273 (2000)). In addition, anti-CCR-3 monoclonal antibodies completely inhibit eotaxin interaction with eosinophils (Heath, H. *et al.*, (1997) J. Clin. Invest. **99** (2), 178-184), while an antibody for the CCR-3 specific chemokine, eotaxin, reduced both bronchial hyperreactivity and lung eosinophilia in an animal model of asthma (Gonzalo et al., J. Exp. Med., **188**, 157-167 (1998). Thus, many lines of evidence indicate that antagonists at the CCR-3 receptor are very likely to be of therapeutic use for the treatment of a range of inflammatory conditions.

A number of patent applications relating to CCR-3 antagonists have published before the filing date of this application. For example, EP 0 903 349, FR 2785902, WO 00/29377, WO 00/31032 and WO 00/31033 (all in the name of F.Hoffmann-La-Roche AG) disclose pyrrolidine, piperidine and piperazine based compounds which are all distinct from the compounds of the present invention.

WO 99/55324, WO 00/04003, WO 00/27800, WO 00/27835, WO 00/27843, WO 00/41685 and WO 00/53172 (all in the name of SmithKline Beecham Corporation) describe a variety of compounds as CCR-3 antagonists which are unrelated to the compounds of the present invention.

WO 00/34278 (Toray Industries Inc.) describe fused triazolo derived compounds as chemokine inhibitors.

WO 00/35449, WO 00/35451, WO 00/35452, WO 00/35453, WO 00/35454, WO 00/35876 and WO 00/35877 (Du Pont Pharmaceuticals Company) describe N-ureidoalkyl and heterocyclic piperidine compounds as CCR-3 antagonists.

WO 00/51607 and WO 00/51608 (Merck & Co. Inc.) describe a series of pyrrolidine modulators of chemokine receptor activity.

WO 00/53600 (Banyu Pharmaceutical Co. Ltd.) describes piperidine derivatives as inhibitors at the CCR-3 receptor.

WO 01/14333 (AstraZeneca UK Ltd.) describe substituted piperidine compounds as modulators of chemokine receptor activity.

EP 0 760 362 (Nisshin Flour Milling Co. Ltd.) describes morpholinoalkylurea derivatives which are disclosed as being useful in the treatment of digestive tract diseases.

JP 04208267A (Mitsui Seiyaku Kogyo KK) also describes morpholinoalkylurea derivatives which are disclosed as being useful as antiemetics, for activating peristalsis and ameliorating gastrointestinal function.

EP 243959A (Dainippon Pharm KK) describes O-substituted N-morpholinyl-alkyl-benzamide derivatives useful as gastrointestinal motility enhancing agents.

J0 1117-882A (Dainippon Pharm KK) describes heterocyclic morpholinyl alkylenyl carboxamide derivatives useful as anti-emetics.

WO 00/71518 (Sepracor Inc) describes morpholinoalkylamide derivatives useful in the treatment of pain, drug addiction and tinnitus.

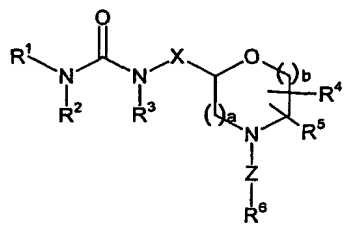
WO 97/48695 and WO 97/48397 (Klinge Pharma Gmbh) describe pyridyl alkane, alkene and/or alkyne acid amide compounds useful as cytostatic, immunomodulatory or immuno-suppressive agents.

Kato *et al.*, (1992) Chem. Pharm. Bull. **40(3)**, 652-660, Kato et al., (1991) J. Med. Chem. **34(2)**, 616-624 and Kato et al., (1990) J. Med. Chem. **33(5)**, 1406-1413 describe a series of morpholine benzamides which are disclosed as being selective and potent gastrokinetic agents.

We have now found a novel group of CCR-3 antagonist compounds which block migration/chemotaxis of eosinophils, consequently effecting anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from eosinophil, basophil and Th2-cell-induced tissue damage in diseases where such cell types are implicated, particularly allergic diseases, including but not limited to bronchial asthma, allergic rhinitis and atopic dermatitis.

In addition to a key role in inflammatory disorders, chemokines and their receptors also play a role in infectious disease. Mammalian cytomegaloviruses, herpes viruses and pox viruses express chemokine receptor homologues, which can be activated by human CC chemokines such as RANTES and MCP-3 (for review see Wells and Schwartz, Curr. Opin. Biotech., 8, 741-748, 1997). In addition, human chemokine receptors, such as CXCR-4, CCR-5 and CCR-3, can act as co-receptors for the infection of mammalian cells by microbes such as human immunodeficiency viruses (HIV). CCR-3 serves as a co-receptor for certain clinical strains of HIV-1 and facilitates viral entry (e.g Choe, H. *et al*, Cell, 1996, **85**, 1135-1148). A key ligand for CCR-3, eotaxin, blocked the process of HIV entry. Thus, chemokine receptor antagonists, including CCR-3 antagonists, may be useful in blocking infection of CCR-3 expressing cells by HIV or in preventing the manipulation of immune cellular responses by viruses such as cytomegaloviruses.

Thus, according to one aspect of the invention, we provide compounds of formula (I):



(I)

wherein:

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, aryl-SO_2-Y^1-, C_{1-6} alkyl-G-Y^1-, heteroaryl-G-aryl-Y^1-, J^1-SO_2-Y^1-, $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, $R^{17}NHCO$-Y^1-, $R^{17}NHSO_2$-Y^1-, C_{2-6} alkynyl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which C_{2-6} alkynyl and C_{2-6} alkynyl-Y^1 may be optionally substituted with a $-OR^{17}$ group, which C_{2-6} alkenyl may be optionally substituted by one or more -$COOR^{17}$ groups and which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl optionally substituted by a hydroxy group;

R^3 represents hydrogen or C_{1-6} alkyl;

or R^1 and R^2 may together with the nitrogen atom to which they are attached form a group of formula J^2 wherein said nitrogen atom substitutes for either X^1 or X^2;

t represents 0 or 1.

X represents ethylen or a group of formula CR^eR^f wherein R^e and R^f independently represent hydrogen or C_{1-4} alkyl or R^e and R^f may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R^4 and R^5 independently represent hydrogen or C_{1-4} alkyl;

Z represents a bond, CO, SO_2, $CR^{10}R^7(CH_2)_n$, $(CH_2)_nCR^{10}R^7$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$, $CHR^7(CH_2)_nCO$, $COCHR^7(CH_2)_n$ or $SO_2CHR^7(CH_2)_n$;

R^6 represents C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, aryl-C_{2-6} alkenyl-, -CN or a group of formula $-Y^2-J^3$;

R^7 represents hydrogen, C_{1-4} alkyl, $CONR^8R^9$ or $COOC_{1-6}$ alkyl;

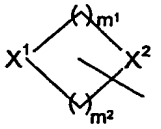
a and b represent 1 or 2, such that a+b represents 2 or 3;

G represents $-SO_2-$, $-SO_2NR^{18}-$, $-NR^{18}SO_2-$, $-NR^{18}CO-$, CO or $-CONR^{18}-$;

n represents an integer from 0 to 4;

M represents a C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl group fused to a monocyclic aryl or monocyclic heteroaryl group;

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{11}, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-COC_{3-8}$ cycloalkyl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{15}R^{16}$, $-Y^3-CONR^{15}R^{16}$, hydroxy, oxo, $-Y^3-SO_2NR^{15}R^{16}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{13}C_{1-6}$ alkyl, $-Y^3-NR^{13}SO_2C_{1-6}$ alkyl, $-Y^3-NR^{13}CONR^{15}R^{16}$, $-Y^3-NR^{13}COOR^{14}$ or $-Y^3-OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen or C_{1-6} alkyl;

R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or R^{15} and R^{16} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring;

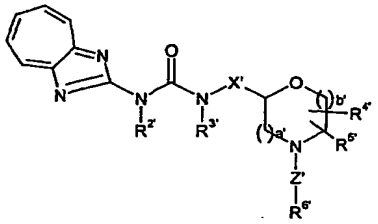
R^{17} and R^{18} independently represent hydrogen or C_{1-6} alkyl;

W represents a saturated or unsaturated, non-aromatic 5-7 membered ring containing between 1 and 3 heteroatoms selected from nitrogen, oxygen or sulphur, optionally substituted with one or more C_{1-6} alkyl, halogen or hydroxy groups;

Y^1, Y^2 and Y^3 independently represent a bond or a group of formula $-(CH_2)_pCR^cR^d(CH_2)_q-$ wherein R^c and R^d independently represent hydrogen or C_{1-4} alkyl or R^c and R^d may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group, and p and q independently represent an integer from 0 to 5 wherein p + q is an integer from 0 to 5;

and salts and solvates thereof.

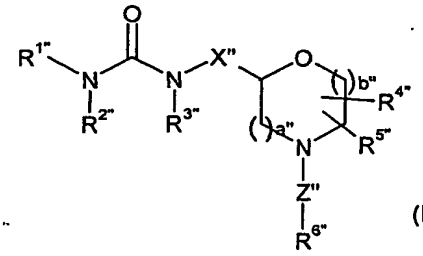
Specific groups of compounds of formula (I) which may be mentioned are those as defined above with the proviso that the compound of formula (I) is not a compound of formula $(I)^a$:



$(I)^a$

wherein $R^{2'}$ represents hydrogen or lower alkyl (specifically C_{1-4} alkyl); $R^{3'}$ represents hydrogen; X' represents methylene or ethylene; a' and b' both represent 1; $R^{4'}$ and $R^{5'}$ both represent hydrogen; and wherein the moiety $-Z'-R^{6'}$ represents halobenzyl (compounds of formula $(I)^a$ are described in JP 04208267A); and/or

the proviso that the compound of formula (I) is not a compound of formula $(I)^b$:



$(I)^b$

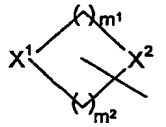
wherein $R^{1''}$ represents a hydrogen atom, a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{3-6} cycloalkylC_{1-4} alkyl group, an aryl group or an arylC_{1-4} alkyl group (particularly wherein aryl

represents phenyl or naphthyl) in which the aryl moiety of the aryl group or arylC_{1-4} alkyl group may be optionally substituted with a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group or an amino group; $R^{2''}$ represents hydrogen; $R^{3''}$ represents hydrogen or C_{1-6} alkyl; X'' represents methylene; a'' and b'' both represent 1; $R^{4''}$ and $R^{5''}$ both represent hydrogen; and wherein the moiety -Z''-$R^{6''}$ represents a C_{1-6} alkyl group, an arylC_{1-4} alkyl group (particularly wherein aryl represents phenyl or naphthyl), a heteroarylC_{1-4} alkyl group (particularly wherein heteroaryl represents 2-pyridyl, 3-pyridyl, 4-pyridyl or 1H-indol-3-yl), an aryloxyC_{2-5} alkyl group or a pyrrolidinylcarbonylC_{1-4} alkyl group in which the aryl moiety of the said groups may be optionally substituted with a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group or an amino group (compounds of formula $(I)^b$ are described in EP0760362A1).

A preferred set of compounds include compounds of formula (I) wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, aryl-SO_2-Y^1-, C_{1-6} alkyl-G-Y^1-, J^1-SO_2-Y^1-, $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, C_{2-6} alkynyl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which C_{2-6} alkynyl and C_{2-6} alkynyl-Y^1 may be optionally substituted with a $-OR^{17}$ group and which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl; and

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{11}, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) -Y^3-aryl, -Y^3-heteroaryl, -Y^3-CO-aryl, -Y^3-CO-heteroaryl, -C_{1-6} alkyl, -Y^3-$COOC_{1-6}$ alkyl, -Y^3-COC_{1-6} alkyl, -Y^3-W, -Y^3-CO-W, -Y^3-$NR^{15}R^{16}$, -Y^3-$CONR^{15}R^{16}$, hydroxy, oxo, -Y^3-$SO_2NR^{15}R^{16}$, -Y^3-SO_2C_{1-6} alkyl, -Y^3-SO_2aryl, -Y^3-SO_2heteroaryl, -Y^3-$NR^{13}C_{1-6}$ alkyl, -Y^3-$NR^{13}SO_2C_{1-6}$ alkyl, -Y^3-$NR^{13}CONR^{15}R^{16}$, -Y^3-

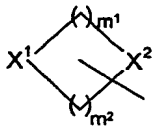
$NR^{13}COOR^{14}$ or $-Y^3-OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

A preferred subset of compounds include compounds of formula (I) wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, -Y^1-J^1, -Y^1-CO-J^1 or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl;

Z represents a bond, CO, $CR^{10}R^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$, $CHR^7(CH_2)_nCO$; and

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, nitrogen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, nitrogen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3, m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when X^2 represents oxygen, nitrogen, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{15}R^{16}$, $-Y^3-CONR^{15}R^{16}$, hydroxy, oxo, $-Y^3-SO_2NR^{15}R^{16}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{13}C_{1-6}$ alkyl, $-Y^3-NR^{13}SO_2C_{1-6}$ alkyl, $-Y^3-NR^{13}CONR^{15}R^{16}$, $-Y^3-NR^{13}COOR^{14}$ or $-Y^3-OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) and references to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-3 hetero atoms selected from nitrogen, oxygen and sulphur. References to 'heteroaryl' may also be extended to include references to mono- and bicyclic heterocyclic aromatic rings containing 4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. pyridinyl, pyrimidinyl, thiophenyl, furanyl, pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl. Further examples of

monocyclic heterocyclic aromatic rings include pyrazinyl, tetrazolyl or imidazolyl. Examples of bicyclic heterocyclic aromatic rings include eg. quinolinyl or indolyl. Further examples of bicyclic heterocyclic aromatic rings include benzimidazolyl. Yet further examples of bicyclic heterocyclic aromatic rings include dihydrobenzofuranyl and pyrrolopyridinyl. Carbocyclic and heterocyclic aromatic rings may be optionally substituted, e.g. by one or more C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, cyano, hydroxy, nitro, amino, W, $-N(CH_3)_2$, $-NHCOC_{1-6}$ alkyl, $-OCF_3$, $-CF_3$, $-COOC_{1-6}$ alkyl, $-OCHF_2$, $-SCF_3$, $-CONR^{19}R^{20}$, $-SO_2NR^{19}R^{20}$ (wherein R^{19} and R^{20} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl), $-NHSO_2CH_3$, $-SO_2CH_3$ or $-SCH_3$ groups. A further substituent of carbocyclic and heterocyclic aromatic rings may be –COOH. Yet further substituents of carbocyclic and heterocyclic aromatic rings may be $-CH_2N(CH_3)_2$ or one or more –SH groups, wherein it will be appreciated that said group may tautomerise to form an =S group.

Examples of group M include tetrahydronaphthalenyl.

Examples of group W include piperidinyl, pyrrolidinyl, morpholinyl and piperazinyl which may be optionally substituted with one or more C_{1-6} alkyl, halogen, or hydroxy groups.

Examples of group J^1 include N-($COOCH_2CH_3$)-piperidin-4-yl, N-(CH_3)-piperidin-4-yl, N-($COCH_3$)-piperidin-4-yl, pyrrolidin-1-yl, tetrahydropyran-4-yl or N-morpholinyl. Further examples of group J^1 include N-(cyclopropylcarbonyl)-piperidin-4-yl, N-(methylsulphonyl)-piperidin-4-yl, thiopyranyl and tetrahydrothienyl.

Examples of group J^2 include (4-phenyl)-piperidin-1-yl, (4-$COOCH_2CH_3$)-piperazin-1-yl, (2-(3-hydroxy-pyrrolidin-1-yl-methyl))-piperidin-1-yl, N-morpholinyl, (4-$N(CH_3)_2$)-piperidin-1-yl, (4-(3-fluorophenyl))-piperazin-1-yl, (4-(4-fluorophenyl))-piperazin-1-yl, (4-pyrimidinyl)-piperazin-1-yl, (4-CH_3)-piperazin-1-yl, (4-$CONH_2$)-piperidin-1-yl, (3,3-dimethyl)-piperidin-1-yl, (4-$COCH_3$)-piperazin-1-yl, (4-(1-pyrrolidinyl-carbonylmethyl))-piperazin-1-yl, (4-hydroxy)-piperidin-1-yl, (4-methyl)-piperidin-1-yl, (4-(2-furanyl-carbonyl))-piperazin-1-yl, (4-benzyl)-piperazin-1-yl or (3-$CH_3SO_2CH_2$-)-morpholin-1-yl. Further examples of group J^2 include thiomorpholinyl, pyrrolidinyl and benzazepinyl.

Examples of group J^3 include indolinyl, which may be optionally substituted.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkylene and alkoxy shall be interpreted similarly.

References to C_{3-8} cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl.

Preferably, R^1 represents C_{1-6} alkyl (particularly propyl), C_{2-6} alkenyl (particularly wherein said C_{2-6} alkenyl is substituted by one or more $-COOR^{17}$ groups, eg. –HC=CH-COOH), C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1- (particularly wherein heteroaryl represents thiazolyl, indolyl, furanyl, dihydrobenzofuran, oxoimidazolyl, isoxazolyl, thienyl, thioxodihydroimidazolyl, tetrazolyl, pyrazinyl, pyrrolopyridinyl), aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1- (particularly wherein aryl represents phenyl and heteroaryl represents thiadiazolyl, pyrazolyl or isoxazolyl), heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1- (particularly wherein aryl represents phenyl), heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1- (particularly wherein C_{1-6} alkyl represents ethyl, propyl, $-CH(CH_3)_2$ or $-C(CH_3)_3$), M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-SO_2-Y^1-, C_{1-6} alkyl-G-Y^1- (particularly wherein C_{1-6} alkyl represents methyl and G represents $-NR^{18}CO-$, $–CONR^{18}-$, $–NR^{18}SO_2-$ or $–SO_2NR^{18}-$), heteroaryl-G-aryl-Y^1- (particularly wherein aryl represents phenyl and heteroaryl represents thiazolyl and G represents $-NR^{18}SO_2-$), J^1-SO_2-Y^1- (particularly wherein J^1 represents 1-pyrrolidinyl), $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, $R^{17}NHCO$-Y^1- (particularly wherein R^{17} represents hydrogen), C_{2-6} alkynyl-Y^1- (particularly -C≡CH or wherein said C_{2-6} alkynyl is substituted with a $–OR^{17}$ group, eg. $HOCH_2$-C≡C-), aryl-CO-Y^1- (particularly wherein aryl represents phenyl), C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups and which C_{2-6} alkynyl-Y^1- may be optionally substituted with a $–OR^{17}$ group.

More preferred R^1 groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups.

Yet more preferably, R^1 represents aryl-Y^1-, heteroaryl-Y^1, aryl-$(O)_t$-aryl-Y^1-, C_{3-8} cycloalkyl-Y^1-, C_{2-6} alkenyl-Y^1- or C_{1-6}alkyl-SO_2-Y^1- especially wherein aryl represents phenyl or naphthyl optionally substituted by one or more C_{1-6} alkyl (especially methyl), halogen (especially chlorine, fluorine and bromine), CH_3O-, CH_3S-, F_2CHO-, $CH_3OC(O)$-, -CN, $-CF_3$, CF_3-S-, CF_3-O-, or $(CH_3)_2N$-, groups, and wherein heteroaryl represents pyridinyl optionally substituted by one or more halogen atoms (especially chlorine) and wherein cycloalkyl represents cyclohexyl. Further preferred substituents of phenyl include $-NHCOCH_3$ and $-CONH_2$. Yet further preferred substituents of phenyl include $–SO_2NH_2$, $-CONHCH_3$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, -COOH, $-CON(CH_3)_2$, $-SO_2CH_3$, $-CONHCH_2CH_3$, -CONHcyclopropyl

and $-SO_2NH$cyclopropyl. Also preferably, R^1 represents C_{2-6} alkynyl-Y^1-. A seri s of particularly preferred compounds are those wherein R^1 represents aryl-Y^1- wherein aryl represents phenyl optionally substituted by one or more C_{1-6} alkyl (especially methyl), halogen (especially chlorine, fluorine and bromine), CH_3O-, CH_3S-, F_2CHO-, $CH_3OC(O)$-, -CN or $-CF_3$ groups. Further most preferred substituents of phenyl include $-NHCOCH_3$ and $-CONH_2$. A yet further most preferred substituent of phenyl includes SO_2NH_2. Most preferably, R^1 will also represent C_{2-6} alkenyl-Y^1- (particularly CH_2=CH-Y^1-), C_{3-8} cycloalkyl-Y^1- (particularly cyclohexyl-Y^1-) and C_{1-6} alkyl-SO_2Y^1- (particularly CH_3SO_2-Y^1-). Also most preferably, R^1 represents C_{2-6} alkynyl-Y^1- (particularly HC≡C-Y^1).

Especially preferred R^1 groups are aryl-Y^1- and heteroaryl-Y^1-, most especially wherein aryl represents phenyl and heteroaryl represents a 6 membered monocyclic heterocyclic aromatic ring (most particularly tetrazolyl) each of which may be optionally substituted as indicated above.

Preferred substituents of heteroaryl include $-CH_3$, $-CONH_2$, $-CH_2N(CH_3)_2$, halogen (particularly chlorine), $-OCH_3$, $-COOCH_3$ and $-NH_2$.

Most especially preferred compounds are those wherein R^1 represents phenyl-Y^1- which phenyl is substituted with a $-CONH_2$ or $-CONHCH_3$ group and tetrazolyl-Y^1- which tetrazolyl is substituted with a methyl group.

Preferably, Y^1 represents a bond or C_{1-6} alkylene, more preferably a bond, methylene or ethylene, propylene, $-C(CH_3)_2$- or $-CH(CH_3)$-, particularly a bond, methylene or ethylene, most preferably a bond or methylene, especially methylene.

Preferably, Y^2 represents a bond.

Preferably, Y^3 represents a bond.

Preferably, R^2 represents hydrogen, methyl or hydroxypropyl, more preferably hydrogen or methyl, especially hydrogen.

Preferably, R^3 represents hydrogen or methyl, especially hydrogen.

Also preferably, R^1 and R^2 together with the nitrogen atom to which they are attached form a group of formula J^2 wherein said nitrogen atom substitutes for either X^1 or X^2.

Preferably, X represents methylene.

Preferably, R^4 and R^5 independently represent hydrogen or methyl. Most preferably, R^4 and R^5 represent hydrogen.

Preferably, Z represents a bond, CO, $CR^{10}R^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$ or $CHR^7(CH_2)_nCO$.

More preferably, Z represents CO, $CHR^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$ or $CHR^7(CH_2)_nCO$, especially CH_2CO, $(CH_2)_2$, $(CH_2)_2S$, $(CH_2)_2O$, $(CH_2)_2OCO$, $(CH_2)_3CO$, CO, CHR^7, particularly CH_2, $CHCH_3$ or CH_2CO, most particularly CH_2 or CH_2CO, especially CH_2.

Preferably, R^6 represents C_{1-6} alkyl, C_{2-6} alkenyl, CN, aryl, heteroaryl or a group of formula $-Y^2-J^3$, more preferably R^6 represents phenyl (optionally substituted with one or more halogen, phenyl or C_{2-6} alkenyl groups), naphthyl, C_{1-6} alkyl, C_{2-6} alkenyl, CN or a 5 membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from O, N or S optionally substituted by halogen or C_{1-6} alkyl. Especially, R^6 represents phenyl (optionally substituted with one or more halogen (especially chlorine, fluorine or iodine), phenyl or 3–$CH=CH_2$ groups), naphthyl, indolinyl, methyl, $-CH=CH_2$, -CN or thiophenyl optionally substituted by halogen (especially chlorine). Most preferred R^6 represents indolinyl (especially indolin-1-yl) or else represents phenyl substituted by one or more halogen (eg. chlorine or fluorine) groups, particularly dichlorophenyl, 3-chlorophenyl, 5-chlorothiophenyl, 4-fluorophenyl and 3,4-difluorophenyl, most particularly dichlorophenyl, especially 3,4-dichlorophenyl.

Preferably, R^7 represents hydrogen, methyl, $COOC_{1-6}$ alkyl or $CONR^8R^9$, more preferably hydrogen, $COOC_{1-6}$ alkyl or $CONR^8R^9$ most preferably hydrogen, COOEt or $CONR^8R^9$, especially hydrogen.

Preferably, R^8 and R^9 represent hydrogen.

Preferably, R^{10} represents hydrogen.

Preferably, R^{11} and R^{12} independently represent hydrogen or methyl.

Preferably, R^{13} and R^{14} independently represent hydrogen or methyl.

Preferably, R^{15} and R^{16} independently represent hydrogen or methyl or R^{15} and R^{16} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring, especially hydrogen or methyl.

Preferably, R^{17} represents hydrogen.

Preferably, R^{18} represents hydrogen.

Preferably, R^{19} and R^{20} independently represent hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, especially hydrogen, cyclopropyl or methyl. Particularly, R^{19} and R^{20} represent hydrogen.

Preferably, R^c represents hydrogen or methyl, particularly hydrogen.

Preferably, R^d represents hydrogen or methyl, particularly hydrogen.

Preferably, a and b both represent 1.

Preferably, n represents 0, 1 or 2.

Preferably, p + q equals an integer from 0 to 2, more preferably, p and q independently represent 0 or 1 such that p + q equals an integer from 0 to 1.

Preferably, t represents 0.

Preferably, W represents pyrrolidinyl or piperidinyl, especially pyrrolidinyl.

Preferably, X^1 represents oxygen, nitrogen or NR^{11}.

Preferably, X^2 represents CH_2, oxygen, nitrogen or NR^{12}.

Preferably, m^1 and m^2 independently represent an integer from 1 to 2, such that $m^1 + m^2$ is in the range from 3 to 4.

Preferably, J^1 represents piperidinyl (particularly piperidin-4-yl) or tetrahydropyranyl (particularly tetrahydropyran-4-yl) optionally substituted by one or two -$COOCH_2CH_3$, -COOtBu, -CH_3, -$COCH_3$, –$SO_2N(CH_3)_2$, -SO_2CH_3, -COPhenyl or 3, 5-dimethylisoxazol-4-ylsulphonyl groups. Also preferably, J^1 represents morpholinyl, thiopyranyl or tetrahydrothienyl which may be optionally substituted as above (particularly dioxidotetrahydrothienyl).

Preferred substituents for J^1 include –CH_2-aryl (particularly wherein aryl represents phenyl optionally substituted with one or more halogen atoms, eg. dichlorophenyl), -COcyclopropyl or -Y^3-SO_2heteroaryl (particularly wherein heteroaryl represents dimethylisoxazolyl).

Preferably, J^2 represents piperidinyl (particularly piperidin-1-yl), morpholinyl (particularly N-morpholinyl) or piperazinyl (particularly piperazin-1-yl) optionally substituted by one or two phenyl, -$COOCH_2CH_3$, -$N(CH_3)_2$, fluorophenyl, -CH_3, -$CONH_2$, -$COCH_3$, -CH_2CO-(N-pyrrolidinyl), hydroxy, -CO-(2-furan), benzyl or -$CH_2SO_2CH_3$. Preferably, J^2 also represents thiomorpholinyl, pyrrolidinyl or benzazepinyl optionally substituted in a similar manner.

Other preferred substituents for J^2 include halogen (particularly fluorine), -$COOCH_2CH_3$, -CO-furoyl, –SO_2CH_3, –pyridinyl-CH_3 or oxo groups.

Preferably, J^3 represents indolinyl, particularly indolin-1-yl.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates,

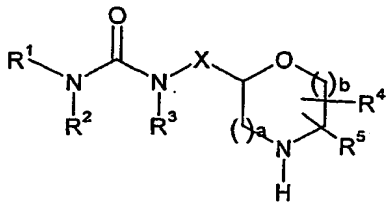
succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates. Examples of solvates include hydrates.

When compounds of formula (I) contain chiral centres, the invention extends to mixtures of enantiomers (including racemic mixtures) and diastereoisomers as well as to individual enantiomers. Generally it is preferred to use a compound of formula (I) in the form of a single enantiomer.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A process according to the invention for preparing a compound of formula (I) comprises:

(a) reacting a compound of formula (II)

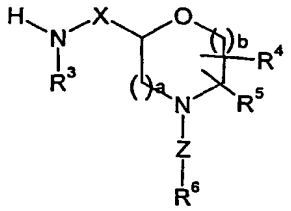


(II)

wherein R^1, R^2, R^3, R^4, R^5, X, a and b are as defined above, or a protected derivative thereof, with a compound of formula

L^1-Z-R^6, wherein Z and R^6 are as defined above and L^1 represents a suitable leaving group; or

(b) forming a compound of formula (I) wherein R^2 represents hydrogen which comprises reacting a compound of formula (III)

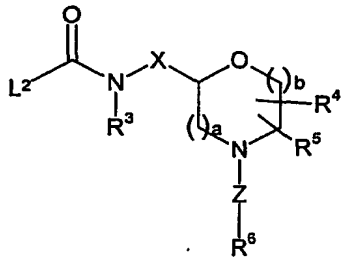


(III)

wherein R^3, R^4, R^5, R^6, Z, X, a and b are as defined above, or a protected derivative thereof, with a compound of formula

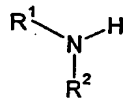
R^1-N=C=O, wherein R^1 is as defined above; or

(c) reacting a compound of formula (IV)



(IV)

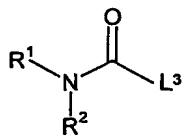
wherein R^3, R^4, R^5, R^6, Z, X, a and b are as defined above or a protected derivative thereof and L^2 represents a suitable leaving group, or a protected derivative thereof, with a compound of formula (V)



(V)

wherein R^1 and R^2 are as defined above or a protected derivative thereof; or

(d) reacting a compound of formula (VI)



(VI)

wherein R^1 and R^2 are as defined above and L^3 represents a suitable leaving group, or a protected derivative thereof, with a compound of formula (III), or a protected derivative thereof; or

(e) deprotecting a compound of formula (I) which is protected; or

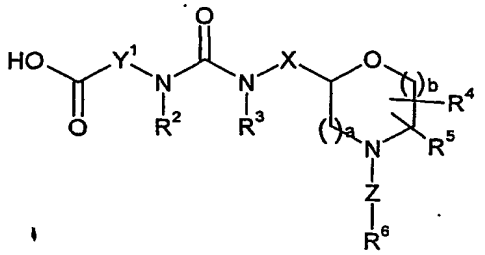
(f) interconversion of other compounds of formula (I).

We also provide a further process according to the invention for preparing a compound of formula (I) which comprises:

(g) forming a compound of formula (I) wherein R^1 and R^2 together with the nitrogen atom to which they are attached form a group of formula J^2 wherein said nitrogen atom substitutes for either X^1 or X^2 which comprises reacting a compound of formula (IV) or a protected derivative thereof with a compound of formula J^2H, provided that the compound of formula J^2H has a free –NH group; or

(h) forming a compound of formula (I) wherein Z represents $CR^{10}R^{7}(CH_2)_n$, wherein R^{10} represents hydrogen, which comprises reacting a compound of formula (II) or a protected derivative thereof with a compound of formula $R^{7}CO(CH_2)_nR^{6}$, followed by reduction of the resultant imine; or

(i) forming a compound of formula (I) wherein R^1 represents C_{1-6} alkyl-G-Y^1-, wherein G represents $-NR^{18}CO-$, which comprises reacting a compound of formula (VII)



(VII)

or a protected derivative thereof wherein R^2, R^3, R^4, R^5, R^6, Y^1 X, Z, a and b are as defined above, with a compound of formula C_{1-6} alkyl-NHR^{18}.

Process (a) may be performed in the presence of an inert solvent eg. N,N-dimethylformamide optionally in the presence of a base such as N,N-diisopropylethylamine at a suitable temperature eg. room temperature. Examples of suitable leaving groups (L^1) include halogen, eg. chlorine.

Process (b) may be performed in the presence of an inert solvent eg dichloromethane at a suitable temperature eg. room temperature.

Processes (c) and (d) may typically be performed in the presence of a suitable base eg. pyridine at a suitable temperature e.g. 110°C, wherein leaving groups L^2 and L^3 may represent 4-nitrophenoxy. Alternatively, when L^2 and L^3 represent 4-nitrophenoxy, suitable conditions may involve the use of N,N-diisopropylethylamine as a suitable base and dichloromethane or N, N-dimethylformamide as a suitable solvent. Alternatively, where L^2 and L^3 are Merrifield resin bound 4-thiophenoxy, processes (c) and (d) may be performed with a suitable additive e.g. N-methylpyrrolidinone in a microwave oven, for example at a power of 600W for 5 min. Other suitable leaving groups include imidazolyl. Wherein L^2 or L^3 represent imidazolyl, suitable conditions comprise the use of 1,1'-carbonyldiimidazole in suitable solvents such as dichloromethane and N,N-dimethylformamide at a suitable temperature, e.g. between 0°C and 22°C.

In process (e), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include sulphonyl (e.g.

tosyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker) or a 2,6-dimethoxy-4-[2-(polystyrylmethoxy)ethoxy]benzyl group, which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

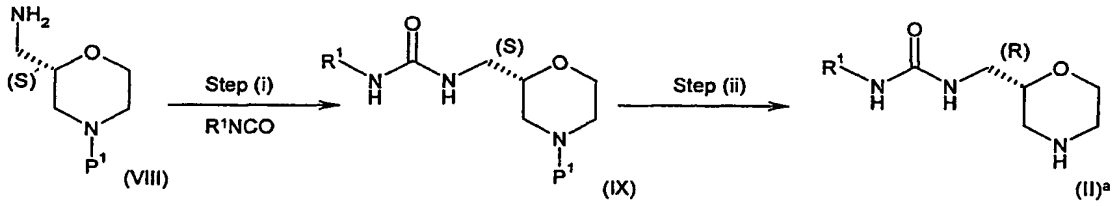
Process (f) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic aromatic substitution, ester hydrolysis or amide bond formation. Alternative conditions for process (f) include t-butoxycarbonyl group addition or removal and sulphonylation.

Process (g) may be performed in an identical manner to the conditions described above for processes (c) and (d).

Process (h) may be performed in the presence of a suitable acid, eg. acetic acid and a suitable reducing agent, eg. sodium triacetoxyborohydride in a suitable solvent, eg. dichloromethane at a suitable temperature, eg. room temperature.

Process (i) may be performed in the presence of a suitable coupling reagent, eg. 1,1'-carbonyldiimidazole and a suitable solvent, eg. N,N-dimethylformamide at a suitable temperature, eg. room temperature.

Compounds of formula (II) as the R-isomer, wherein R^2 and R^3 both represent hydrogen, X represents methylene, a and b represent 1 and R^4 and R^5 both represent hydrogen may be prepared according to the following process:



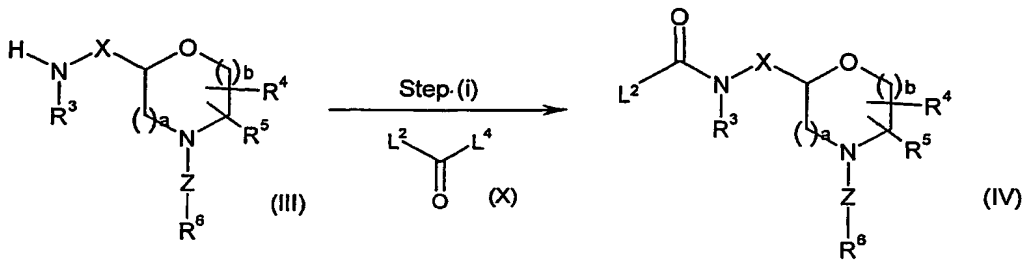
wherein R^1 is as defined above and P^1 is a suitable protecting group, eg. benzyl.

Compounds of formula (VIII) may be prepared as described in EP0995746.

Step (i) typically comprises the use of an inert solvent eg dichloromethane at a suitable temperature eg. room temperature. Step (ii) typically comprises a simple deprotection reaction, eg. which may comprise the use of 10% palladium on activated carbon in the presence of ammonium formate and a suitable solvent, eg. ethanol.

Compounds of formula (II)[a] as the S-isomer, wherein R^1 is as defined above, may be prepared by an analogous process.

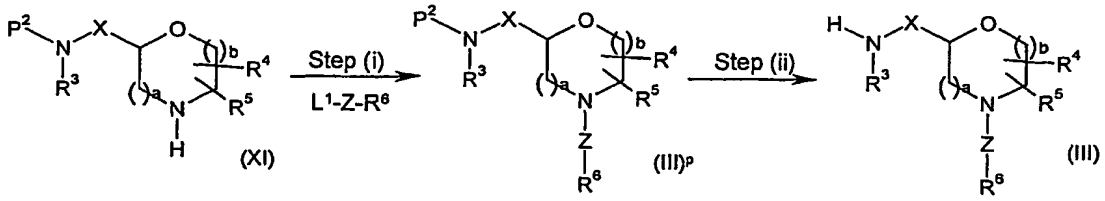
Compounds of formula (IV) may be prepared according to the following process:



wherein R^3, R^4, R^5, R^6, X, a, b and Z are as defined above and L^2 represents a suitable leaving group as defined above eg. 4-nitrophenoxy or Merrifield resin bound 4-thiophenoxy and L^4 represents a leaving group more labile than L^2 eg. chlorine or 4-nitrophenoxy. When L^2 represents 4-nitrophenoxy and L^4 represents chlorine, step (i) may be carried out in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine at a suitable temperature such as room temperature. When L^2 represents Merrifield resin bound 4-thiophenoxy and L^4 represents 4-nitrophenoxy, step (i) may be carried out in a suitable solvent such as N,N-dimethylformamide at a suitable temperature such as room temperature. Alternatively L^2 and L^4 may represent imidazole, wherein step (i) may be carried out with 1,1'-carbonyldiimidazole, in a suitable solvent e.g. a mixture of dichloromethane and N,N'-dimethylformamide at a suitable temperature e.g. between 0°C and 22°C .

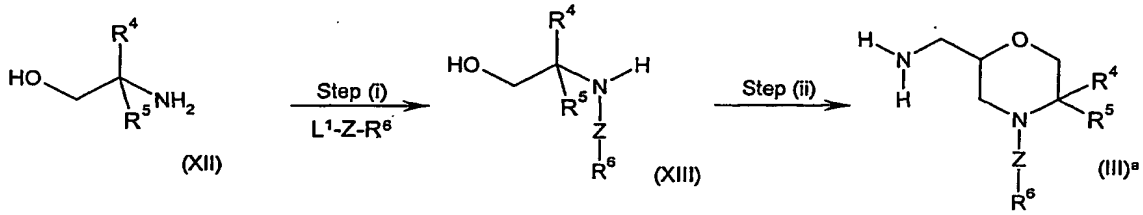
Compounds of formula (III) may be used in protected form, eg. wherein the amine group is protected when R^3 represents hydrogen. Suitable protecting groups are among those described above.

Compounds of formula (III) may be prepared according to the following process:



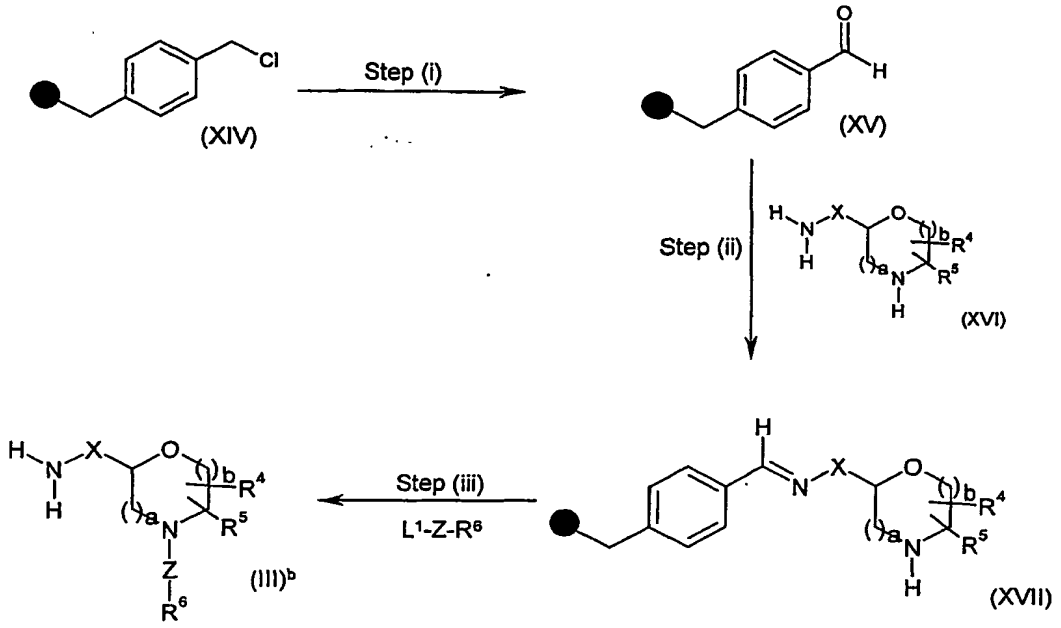
wherein R^3, R^4, R^5, R^6, X, a, b and Z are as defined above and L^1 represents a suitable leaving group eg. chlorine and P^2 represents a suitable protecting group eg. one mentioned above, such as $-COCF_3$. Step (i) comprises the use of a suitable solvent eg. N,N-dimethylformamide in the presence of suitable reagents eg. sodium iodide and potassium carbonate at a suitable temperature eg. room temperature. Step (ii) comprises deprotection under conventional conditions appropriate for the protecting groups. When P^2 represents $-COCF_3$, deprotection may be achieved by the use of water and methanol in the presence of potassium carbonate at room temperature. Compounds of formula (III) wherein Z represents $CR^{10}R^7(CH_2)_n$ (wherein R^{10} represents hydrogen), may also be prepared by reductive amination of compounds of formula (XI) in an analogous manner to that described in process (h) above.

Compounds of formula (III) wherein R^3 represents hydrogen, X represents methylene, a and b represent 1 and R^4 and R^5 are both attached to the morpholine ring at the 5-position may be prepared according to the following process:



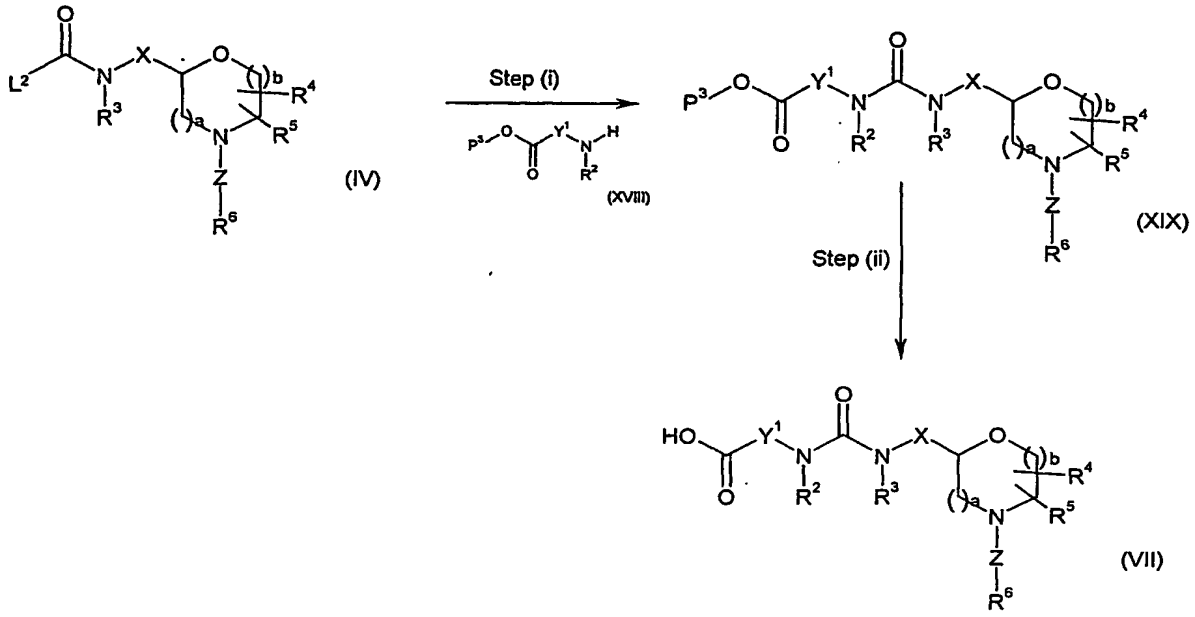
wherein R^6 and Z are as defined above and L^1 represents a suitable leaving group eg. chlorine. Step (i) comprises heating in the absence of solvent at between 50 and 60°C. Step (ii) comprises heating with 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione at 80°C under nitrogen, followed by stirring with concentrated sulphuric acid at 150°C.

Compounds of formula (III) wherein R^3 represents H may be prepared according to the following process:



wherein R^4, R^5, R^6, X, a, b and Z are as defined above and L^1 represents a suitable leaving group eg. chlorine. Step (i) comprises heating a compound of formula (XIV; Merrifield Resin) with sodium carbonate in a suitable solvent eg. dimethylsulphoxide at a suitable temperature eg. 150°C. Step (ii) comprises reacting a compound of formula (XV) with a compound of formula (XVI) in the presence of a suitable solvent eg. tetrahydrofuran at a suitable temperature eg. room temperature. Step (iii) comprises the use of suitable solvent eg. N,N-dimethylformamide and a suitable base eg. N,N-diisopropylethylamine at a suitable temperature eg. 70°C, followed by deprotection under conventional conditions appropriate for the Merrifield resin protecting group eg. acid catalysed hydrolysis.

Compounds of formula (VII) may be prepared according to the following process:



wherein R^2, R^3, R^4, R^5, R^6, Y^1, Z, X, a and b are as defined above, L^2 represents a suitable leaving group, eg. 4-nitrophenoxy and P^3 represents a suitable protecting group eg. C_{1-6} alkyl, preferably t-butyl.

Step (i) typically comprises the use of a suitable base, eg. N,N-diisopropylethylamine and a suitable solvent, eg. dichloromethane at a suitable temperature, eg. room temperature.

Step (ii) typically comprises the use of a suitable acidic reagent, eg. 4M hydrogen chloride in dioxane at a suitable temperature, eg. room temperature.

Compounds of formula (V), (VI), (VIII), (X), (XI), (XII), (XIV), (XVI) and (XVIII) are either known or may be prepared in accordance with known procedures.

Compounds of formula L^1-Z-R^6, R^1N=C=O, $R^7CO(CH_2)_nR^6$, C_{1-6} alkyl-NHR^{18}, and J^2-H are also either known or may be prepared in accordance with known procedures.

Compounds of formula (II) may be prepared in accordance with processes analogous to those described above for compounds of formula (I), employing standard protecting group chemistry. For example, employing suitable protection for the morpholine NH, such as t-butoxycarbonyl protection.

Compounds of formula (II), (III), (IV) and (VII) in protected and unprotected forms and salts and solvates thereof also form an aspect of the invention.

Compounds of the invention may be tested for in vitro and in vivo biological activity in accordance with the following assays:

(a) CCR-3 Binding Assay

A CCR-3 competition binding SPA (scintillation proximity assay) was used to assess the affinity of novel compounds for CCR-3. Membranes prepared from K562 cells stably expressing CCR-3 (2.5μg/well) were mixed with 0.25mg/well wheat-germ agglutinin SPA beads (Amersham) and incubated in binding buffer (HEPES 50 mM, $CaCl_2$ 1 mM, $MgCl_2$ 5 mM, 0.5% BSA) at 4°C for 1.5 hr. Following incubation, 20 pM of [^{125}I] eotaxin (Amersham) and increasing concentrations of compound (1pM to 30μM) were added and incubated in a 96 well plate for 2 hr at 22°C then counted on a Microbeta plate counter. The total assay volume was 100 μl. Competition binding data were analysed by fitting the data with a four parameter logistic equation. Data are presented as the mean pIC_{50} values (negative logarithm of the concentration of compound which inhibits [^{125}I]eotaxin binding by 50%) from at least two experiments.

(b) Eosinophil chemotaxis Assay.

Compounds were evaluated for their inhibitory effect on eosinophil chemotaxis. Eosinophils were purified from human peripheral blood by standard CD16 cell depletion using a Miltenyi cell separation column and a magnetic Super Macs magnet as previously described (Motegi & Kita, 1998; J.Immunology. 161:4340-6). Cells were re-suspended in RPMI 1640/10% FCS solution and incubated with calcein-AM (Molecular Probes) at 37°C for 30 mins. Following incubation, the eosinophils were centrifuged at 400g for 5 min and re-suspended in RPMI/FCS at 2.2 million/ml. Cells were then incubated in the presence of increasing concentration of compounds (1 pM to 30 μM) at 37°C for 30 mins. For control responses cells were incubated with RPMI/FCS only. The agonist eotaxin (either a concentration response curve or for the functional inhibition curves an EC_{80} concentration) was added to the lower chamber of a 96 well chemotaxis plate (5 μm filter: Receptor Technologies). Eosinophils (50 μl of 2 million/ml cells) were added to the top chamber of the filter plate and incubated at 37°C for 45 mins. Cells remaining on top of the chemotaxis filter were removed and the number of eosinophils which had migrated were quantified by reading the plate on a fluorescent plate reader. Inhibition curves for the effect of compounds on eosinophil chemotaxis were analysed by fitting the data with a four parameter logistic equation. Functional pK_i values (fpK_i) were generated using the equation below (Lazareno & Birdsall, 1995. Br.J.Pharmacol 109: 1110-9).

$$fpKi = \frac{IC_{50}}{1 + \left[\frac{[Agonist]}{EC_{50}}\right]}$$

(c) Guinea-pig Ovalbumin Model

Inhibition of Eosinophil Infiltration and Hyper-Reactivity in the Guinea Pig

In a method based on that described by Danahay *et al.*, 1997, ovalbumin sensitised guinea pigs were dosed with mepyramine (30mg kg^{-1} ip) to protect against anaphylactic bronchospasm. Test compounds, dissolved in 10% DMSO and 90% PEG200, were given by the oral route, 30 minutes before ovalbumin challenge (10 minutes breathing of an aerosol generated from a 0.5% solution of ovalbumin). Hyper-reactivity of the airways to the thromboxane mimetic U46619, was measured 24 hours after ovalbumin challenge in un-restrained animals using a whole body plethysmograph (Buxco Ltd., USA). The guinea pigs were then sacrificed and the lungs lavaged. Total and differential leukocyte counts were then obtained for the bronchoalveolar lavage fluid and the percentage reduction in eosinophil accumulation determined (Sanjar *et al.*, 1992). Data was presented as the inhibitory effect of the specified dose expressed as a percentage of the vehicle control response.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as bronchitis (including chronic bronchitis), asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD) and rhinitis. Another disease of the respiratory tract in which the compounds of the invention have potentially beneficial effects is sinusitis. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure. Furthermore, compounds of the invention may be used to treat nephritis, skin diseases such as psoriasis, eczema, allergic dermatitis and hypersensitivity reactions and diseases of the central nervous system which have an inflammatory component eg. Alzheimer's disease, meningitis, multiple sclerosis and AIDS dementia. Compounds of the present invention may also be of use in the treatment ofnasal polyposis, conjunctivitis or pruritis. Additionally, the compounds of the present invention may be of use in the treatment of viral diseases such as HIV.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiovascular conditions such as atherosclerosis,

peripheral vascular disease and idiopathic hypereosinophilic syndrome. Other diseases for which the compounds of the present invention may be beneficial are other hypereosinophilic diseases such as Churg-strauss syndrome. Additionally, eosinophilia is commonly found in parasitic diseases, especially helminth infections, and thus the compounds of the present invention may be useful in treating inflammation arising from hyper-eosinophilic states of diseases such as hydatid cyst (Echinococcus sp.), tapeworm infections (Taenia sp.), blood flukes (schistosomiasis), and nematode (round worms) infections such as:- Hookworm (Ancylostoma sp.), Ascaris, Strongyloides, Trichinella, and particularly lymphatic filariasis including Onchocerca, Brugia, Wucheria (Elephantiasis).

Compounds of the invention may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis. Preferred diseases of principle interest include asthma and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis. Further diseases also of principle interest include inflammatory diseases of the gastrointestinal tract such as inflammatory bowel disease.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful as pharmaceuticals, in particular as anti-inflammatory agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as pharmaceuticals, particularly in the treatment of patients with inflammatory conditions, eg. asthma or rhinitis.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory conditions, eg. asthma or rhinitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition eg. asthma or rhinitis, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in anti-inflammatory therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, parenteral or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in

multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or beta adrenergic agents (such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof), anti-histamines (eg methapyrilene or loratadine) or antiinfective agents (eg. antibiotics, antivirals).

It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more preferably 0.01 to 100mg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen.

The compounds of the invention have the advantage that they may be more efficacious, show greater selectivity, have fewer side effects, have a longer duration of action, be more bioavailable when administered by the oral route, have more ready and economic synthesis, or have other more desirable properties than similar known compounds.

The invention may be illustrated by reference to the following examples:

Examples

General experimental details

Standard Automated Preparative HPLC column, conditions and eluent

Automated preparative high performance liquid chromatography (autoprep. HPLC) was carried out using a Supelco+ 5μm (100mm x 22mm internal diameter) column eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water and (ii) 0.1% trifluoroacetic acid in acetonitrile, the eluent being expressed as the percentage of (ii) in the solvent mixture, at a flow rate of 4ml per minute.

Mass Directed Automated Preparative HPLC column, conditions and eluent

Mass directed automated preparative high performance liquid chromatography was carried out using an LCABZ+ 5μm (5cm x 10mm internal diameter) column, employing gradient elution using two solvent systems, (A) 0.1% formic acid in water, and (B) 95% acetonitrile and 0.5% formic acid in water, at a flow rate of 8ml min^{-1}. Mass spectrometry was carried out using a VG Platform Mass Spectrometer, with an HP1100 Diode Array Detector and Accurate Flow Splitter.

LC/MS System

Three alternative Liquid Chromatography Mass Spectroscopy (LC/MS) Systems were used:

System A

This system used an 3μm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents:A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 3 ml per minute. The following gradient protocol was used: 100% A for 0.7mins; A+B mixtures, gradient profile 0 – 100% B over 3.5mins; hold at 100%B for 1.1mins; return to 100% A over 0.2mins.

System B

This system used an 3μm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents:A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 1 ml per minute. The following gradient protocol was used: 100% A for 1.0min; A+B mixtures, gradient profile 0 – 100% B over 9.0mins; hold at 100%B for 3.0mins; return to 100% A over 2.0mins.

System C

This system used an 3μm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents:A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 1 ml per minute. The following gradient protocol was used: 100% A for 2.0mins; A+B mixtures, gradient profile 0 – 100% B over 20mins; hold at 100%B for 5.0mins; return to 100% A over 2.0mins; hold at 100% A for 1.0mins.

All LC/MS systems used a micromass spectrometer, with electrospray ionisation mode, positive and negative ion switching, mass range 80-1000 a.m.u.

Thermospray Mass Spectra

Thermospray Mass Spectra were determined on a HP 5989A engine mass spectrometer, +ve thermospray, source temperature 250°C, probe temperatures 120°C (stem), 190°C (tip), detection mass range 100-850 a.m.u. Compounds were injected in 10µl of a mixture of solvents comprising 65% methanol and 35% 0.05M aqueous ammonium acetate, at a flow rate of 0.7ml/min.

Normal Phase Automated Preparative HPLC Column - conditions

Normal phase automated preparative high performance liquid chromatography (normal phase autoprep HPLC) was carried out using a Nucleosil silica 5µm (100mm x 20mm internal diameter) column eluted with an ethyl acetate:heptane two-step gradient (i) 0% to 25% ethyl acetate over 7min followed by (ii) 25% to 100% ethyl acetate over 5.5min; at a flow rate of 30ml/min.

Normal phase analytical HPLC method

Normal phase automated analytical high performance liquid chromatography (normal phase analytical HPLC) was carried out using a Nucleosil silica 3µm (150mm x 4.6mm internal diameter) column eluted with an ethyl acetate:heptane two-step gradient (i) 0% to 40% ethyl acetate over 7 min followed by (ii) 40% to 100% ethyl acetate over 2.5 min; at a flow rate of 2ml/min.

Standard chiral analytical HPLC system

This system used a 250 x4.6mm Chiralpak AD 10µm column, eluting with absolute ethanol:heptane mixtures at a flow rate of 1ml per minute, with UV detection at 215nm.

Standard chiral preparative HPLC system

This system used a Chiralpak AD column (2cm x 25cm), eluting with absolute ethanol:heptane mixtures (15ml/min over 25mins, UV detection at 215nm).

Solid phase extraction (ion exchange)

'SCX' refers to Isolute Flash SCX-2 sulphonic acid solid phase extraction cartridges.

Organic/Aqueous phase separation with hydrophobic frits

'Hydrophobic frit' refers to a Whatman polypropylene filter tube fitted with a PTFE frit, pore size 5.0µm.

All temperatures are in °C

Intermediates

Intermediate 1: 2,2,2-Trifluoro-N-(morpholin-2-ylmethyl)acetamide

To a stirred solution of morpholin-2-ylmethylamine (3.1g) in methanol (70ml) under nitrogen was added an ethereal solution of ethyl-α,α,α-trifluoroacetate (5ml in 20ml ether) which had been washed with saturated aqueous sodium bicarbonate, water and brine, and dried. The mixture was stirred for 30 min at 22°C before removal of all volatiles in vacuo. The residue was dissolved in methanol (10ml) and the volatiles again removed in vacuo to give the title compound as a white crunchy foam (4.9g).

Thermospray Mass Spectrum *m/z* 213 [MH^+].

Intermediate 2: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2,2,2-trifluoroacetamide

To a stirred solution of Intermediate 1 (3.3g) in N,N-dimethylformamide (50ml) under nitrogen was added potassium carbonate (2.46g) and sodium iodide (2.12g). A solution of 3,4-dichlorobenzyl chloride (2ml) in N,N-dimethylformamide (10ml) was added dropwise to the mixture. The mixture was stirred at 22°C for 18h before the volatiles were removed in vacuo. The residue was partitioned between dichloromethane (100ml) and saturated aqueous sodium carbonate solution (50ml). The organic phase was subsequently washed with additional saturated aqueous sodium carbonate solution (2 x 50ml) and water (50ml) before drying over magnesium sulphate, filtering and evaporation of the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 25% ethyl acetate in cyclohexane, to give the title compound as a colourless oil (2.97g).

LC/MS (System A) R_t 2.63 min, Mass Spectrum *m/z* 371 [MH^+].

Intermediate 3: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine

To a stirred solution of Intermediate 2 (2.97g) in methanol (15ml) and water (5ml) was added potassium carbonate (5.53g). The mixture was stirred at 22°C for 18h before the methanol was removed in vacuo. Water (25ml) was added and the mixture extracted with ethyl acetate (3 x 30ml). The combined organic phases were washed with water (5ml) and saturated aqueous sodium chloride solution (10ml) before drying over sodium sulphate, filtering and evaporation of the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 75:8:1 dichloromethane/ethanol/0.880 ammonia solution. The required fractions were combined and the solvent evaporated in vacuo to give the title compound as a colourless oil (1.85g).

LC/MS (System A) R_t 1.77 min, Mass Spectrum *m/z* 275 [MH^+].

Intermediate 3: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine (alternative synthesis)

A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (Chem Abs No. 40172-06-3, 0.980g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (1.10g) was heated at 80°C under nitrogen

for 3h. The resulting solid mass was treated with concentrated sulphuric acid (1.5ml) then stirred at 150°C for 24h. The mixture was treated with water (100ml) then washed with ethyl acetate (2x100ml). The dark aqueous phase was basified to ~pH 12 using 5M aqueous sodium hydroxide, then extracted with ethyl acetate (2x100ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (1.02g).

LC-MS (System A): Rt 1.6min.

Intermediate 3A: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine salt with para-toluenesulphonic acid 1:1

A solution of 2-[(3,4-dichlorobenzyl)amino]ethanol (2.25g) and 2-chloroacrylonitrile (1.0ml) in tetrahydrofuran (3ml) was heated at 40°C for 66h. The solvent was evaporated in vacuo to leave a gum. The residue was redissolved in tetrahydrofuran (20ml) and cooled to 0-5°C. Potassium tert-butoxide (1.2g) was added portionwise to this solution over 10min and the mixture was stirred at 0-5°C for a further 45min. The mixture was diluted with water (20ml) and ethyl acetate (20ml), the phases were separated and the organic phase was washed with 20% w/w aqueous sodium chloride solution. The organic phase was dried over sodium sulfate and the solvent was evaporated in vacuo to leave a gum (2.75g).

A portion of this gum (0.22g) in tetrahydrofuran (1ml) was treated dropwise with a 1M solution of borane.tetrahydrofuran complex in tetrahydrofuran (2.44ml) at 15-25°C. The mixture was stirred at 15-25°C for 16h, and methanol (3ml) was added dropwise. The mixture was stirred for a further 5h and the solvent was evaporated in vacuo. The residue was redissolved in ethyl acetate (4ml) and p-toluenesulfonic acid monohydrate (0.123g) was added. The mixture was heated at 50°C for 20min, and the suspension was cooled to 15-25°C and stirred for 15min. The mixture was filtered, washed with ethyl acetate and dried to give the title compound (0.123g) as a white solid.

LC/MS (System A) R_t 1.75 min. Mass spectrum *m/z* 275/277 [MH^+]

Intermediate 4: Benzyl 2-{[(trifluoroacetyl)amino]methyl}morpholine-4-carboxylate

To a stirred solution of Intermediate 1 (6.37g) in methanol (250ml) under nitrogen was added benzylchloroformate (4.7ml) and triethylamine (6.3ml). The mixture was stirred at 22°C for 1h before the volatiles were removed in vacuo. The residue was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 33% ethyl acetate in cyclohexane, to give the title compound as a white solid (4.4g).

LC/MS (System A) R_t 3.22 min, Mass Spectrum *m/z* 347 [MH^+].

Intermediate 5: Benzyl 2-(aminomethyl)morpholine-4-carboxylate

To a stirred solution of Intermediate 4 (4.4g) in 1:1 methanol/water (300ml) was added potassium carbonate (17.5g). The mixture was stirred at 22°C for 36h before the volatiles were evaporated in vacuo. The residue was dissolved in water and the solution extracted with dichloromethane (x 3). The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and filtered before evaporation of the solvent in vacuo. The residue was dissolved in methanol and purified by solid phase extraction (Isolute SCX sulphonic acid column), initially washing the cartridge with methanol before eluting with 10% 0.880 ammonia solution in methanol to give thetitle compound as a colourless oil (2.27g).

LC/MS (System A) R_t 2.07 min, Mass Spectrum *m/z* 251 [MH^+].

Intermediate 6: Benzyl 2-[({[(4-chlorophenyl)amino]carbonyl}amino)methyl]morpholine-4-carboxylate

To a stirred solution of Intermediate 5 (2.0g) in dichloromethane (100ml) was added 4-chlorophenylisocyanate (1.35g). The mixture was stirred at 22°C for 18h before 10% 0.880 ammonia solution in methanol (10ml) was added. Stirring was continued for a further 30 min before the solvent was removed in vacuo. The residue was purified by Biotage flash chromatography on silica gel, eluting with 33% ethyl acetate/cyclohexane; further purification by Biotage flash chromatography on silica gel, eluting with 500:8:1 dichloromethane/ethanol/0.880 ammonia solution gave the impure title compound as a buff solid (3.6g).

LC/MS (System A) R_t 3.41 min, Mass Spectrum *m/z* 404 [MH^+].

Intermediate 7: N-(Morpholin-2-ylmethyl)-N'-phenylurea

A suspension of 10 % palladium on carbon (1.5g) and Intermediate 6 (3.2g) in ethyl acetate (250ml) was stirred vigorously under hydrogen at 1 atmosphere and 22°C for 20h. The catalyst was filtered off and the volatiles were removed in vacuo. The procedure was repeated with a further portion of the catalyst (1g) for a further 24 h before filtration and solvent evaporation in vacuo. Purification of the residue by Biotage flash chromatography on a 90g silica cartridge, eluting with 100:8:1 dichloromethane/ethanol/0.880 ammonia solution, gave the title compound as a colourless oil (1.6g). LC/MS (System A) R_t 1.39 min, Mass Spectrum *m/z* 236 [MH^+].

Intermediate 8: tert-Butyl 2-[({[(4-chlorophenyl)amino]carbonyl}amino)methyl]morpholine-4-carboxylate

To a stirred solution of tert-butyl 2-(aminomethyl)morpholine-4-carboxylate (Prepared as described in EP 0 468231, 2.4g) in dichloromethane (100ml) was added 4-

chlorophenylisocyanate (1.87g). The mixture was stirred at 22°C for 16h before 10% 0.880 ammonia solution in methanol was added. Stirring was continued for a further 30 min before the solvent was removed in vacuo to give the title compound as a white foam (3.98g). LC/MS (System A) R_t 3.19 min, Mass Spectrum *m/z* 370 [MH^+].

Intermediate 9: N-(4-Chlorophenyl)-N'-(morpholin-2-ylmethyl)urea

Intermediate 8 (1.9g) was stirred in 4.0M hydrogen chloride in 1,4-dioxane (40ml) at 22°C for 30min. The solvent was removed in vacuo and the residue was purified by solid phase extraction (Isolute SCX sulphonic acid column), eluting with methanol followed by 10% 0.880 NH_3 solution in methanol, to give the title compound as a cream foam (1.15g). LC/MS (System A) R_t 2.03 min, Mass Spectrum *m/z* 270 [MH^+].

Intermediate 10: 4-Nitrophenyl [4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate

Triethylamine (0.09ml) was added to solution of Intermediate 3 (0.150g, 0.545mmol) in dichloromethane (3ml) with stirring at 20°C under nitrogen. The solution was cooled to 0°C and a solution of 4-nitrophenyl chloroformate (0.121g) in dichloromethane (1ml) was added drop-wise. The resultant mixture was stirred for 4h at 0°C. The solution was allowed to warm to 20°C, washed with brine (4ml), dried ($MgSO_4$), and concentrated in vacuo. Purification by Biotage flash chromatography on silica gel, eluting with 35% ethyl acetate in cyclohexane, gave the title compound as a pale yellow solid (0.119g). LC/MS (system A) R_t 3.01min, Mass Spectrum *m/z* 441 [MH^+].

Intermediate 11: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine

Intermediate 3 (racemic mixture, 8g) was separated into its single enantiomers by preparative chiral-HPLC. The separation was carried out using a 2" x 22cm Chiralpak AD 20µm column, Merck self pack DAC system, eluting with 95:5:0.1 (v/v) heptane : absolute ethanol: diethylamine (flow rate: 55ml/min over 40min, UV detection 225nm); sample load preparation: 400mg sample in 20ml 3:2 (v/v) absolute ethanol: system eluent.

The title compound (2.49g) was obtained as follows: preparative HPLC retention time 23.0 min.

Intermediate 11A: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with D-tartaric acid 1:1

35% Hydrazine in water (1.8ml) was added to a slurry of Intermediate 42 (5g) in industrial methylated spirits (75ml), and the mixture was heated to reflux. Chloroform (75ml) was added and the mixture was heated under reflux for 65h. The reaction mixture was cooled to 0-4°C and allowed to stand for 15min. The by-product phthalhydrazide was removed by vacuum filtration and washed with chloroform (50ml). The filtrate was washed with water

(50ml, 25ml), dried ($MgSO_4$), and the solvent evaporated in vacuo to give an oil. This was dissolved in methanol (20ml), which was evaporated in vacuo to give an oil. The oil was dissolved in methanol (100ml) and D-tartaric acid (1.05g) was added. The mixture was heated to and maintained at reflux for 30min. The solution was cooled to 45-50°C, then seeded. The slurry was held at this temperature for 30min, then cooled to 0-4°C and allowed to stand for 30min. The product was isolated by filtration to give the title compound as a white solid (2.59g).

A sample of the crude D-tartrate salt (500mg) was dissolved in water (1.4ml). Methanol (23ml) was added to give a slurry which was heated to reflux to give a solution. The mixture was stirred at reflux for 30min, then cooled slowly, seeding at 55°C. The resultant slurry was cooled to 0-4°C and allowed to stand 30min. The product was isolated by filtration to give the title compound as a white solid (0.355g).

ee: 91.6%ee

LC/MS (System A) R_t 1.75 min. Mass spectrum *m/z* 275/277 [MH^+]

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Intermediate 11A (Alternative Procedure): 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with D-tartaric acid 1:1

Intermediate 3 (0.613g) was dissolved in methanol (12.3ml). D-Tartaric acid (0.335g) was added and the slurry was heated to reflux for 50min. The mixture was allowed to cool to 0-5°C and the precipitate isolated by filtration to give the title compound as a white solid (0.4g).

ee: 76%ee

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Intermediate 12: 1-[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine

Intermediate 12 was prepared in an analogous manner to Intermediate 11 yielding the title compound (2.24g) as follows: preparative HPLC retention time 27.8 min.

Intermediate 12A: 1-[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with L-tartaric acid 1:1

Intermediate 3 (0.500g) was dissolved in methanol (5ml). L-Tartaric acid (0.273g) was added and the mixture was heated to ~65°C to give a milky slurry, and maintained at this temperature for 1h. Further methanol (5ml) was added and the mixture left to cool slowly to 15-25°C, then cooled further to 0-4°C. The mixture was stirred for 30min at this temperature and the product isolated by filtration to give the title compound as a white solid (0.38g).

ee: 78%

LC/MS (System A) R_t 1.75 min. Mass spectrum *m/z* 275/277 [MH^+]

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 10.5min.

Intermediate 13: 4-Nitrophenyl [(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate

Intermediate 13 was prepared in an analogous manner to Intermediate 10 from Intermediate 11 (0.225g) and 4-nitrophenylchloroformate (0.182g) to yield the title compound (0.2g).

LC-MS (System A) Rt 3.1mins. Mass Spectrum *m/z* 441 [MH^+].

Intermediate 14: 4-Nitrophenyl [(2R)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate

Intermediate 14 was prepared in an analogous manner to Intermediate 10 from Intermediate 12 (0.21g) and 4-nitrophenylchloroformate (0.17g) to yield the title compound (0.23g).

LC-MS (System A) Rt 3.09mins. Mass Spectrum *m/z* 441 [MH^+].

Intermediate 15: tert-Butyl 4-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}piperidine-1-carboxylate

Intermediate 15 was prepared in an analogous manner to Example 43 using tetrahydrofuran as solvent, without base, to give the title compound as a white solid (0.157g).

LC/MS (System A) Rt 2.92min, Mass spectrum *m/z* 501 [MH^+].

Intermediate 16: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-piperidin-4-ylurea hydrochloride

Intermediate 15 (0.157g) was stirred in dioxane (4ml) containing 4.0M hydrogen chloride in dioxane (0.78ml) for 16h, at 23°C under nitrogen. The solvent was removed in vacuo, azeotroped with dichloromethane (20ml), triturated in ether and dried under vacuum to give the title compound as a pale yellow solid (0.12g).

LC/MS (System A) Rt 2.02min, Mass spectrum *m/z* 401 [MH^+].

Intermediate 17 tert-butyl 4-({[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)piperidine-1-carboxylate

Intermediate 17 was made in an analogous manner to that of Example 57.

LC-MS (System A) Rt 2.72mins Mass Spectrum *m/z* 515 [MH^+].

Intermediate 18: N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(piperidin-4-ylmethyl)urea dihydrochloride

Intermediate 17 (0.390g) was stirred in 4.0M hydrogen chloride in dioxane (4ml) for 2h, at 23°C under nitrogen. The solvent was removed in vacuo, azeotroped with dichloromethane (20ml), and dried under vacuum to give the title compound as a pale yellow solid, (0.33g).

LC/MS (System A) Rt 1.84 min, Mass spectrum *m/z* 415 [MH^+].

Intermediate 19 [(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methylamine

Intermediate 19 was made in an analogous manner to that of Intermediate 11

Preparative HPLC retention time 26.1min

Intermediate 20 [(2S)-4-(2,3-dichlorobenzyl)morpholin-2-yl]methylamine

Intermediate 20 was made in an analogous manner to that of Intermediate 11

Preparative HPLC retention time 25.3min

Intermediate 21 [(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methylamine

Intermediate 21 was made in an analogous manner to that of Intermediate 11

Preparative HPLC retention time 28.3min

Intermediate 22: 4-Nitrophenyl prop-2-ynylcarbamate

Propargylamine (0.017ml) and triethylamine (0.38ml) in dichloromethane (2ml) were added dropwise to p-nitrophenylchloroformate (0.55g) in dichloromethane (3ml) at 0°C. The solution was stirred for 1h at this temperature then at 23°C for 5h. The solvent was removed in vacuo and the residue purified by solid phase extraction (10g silica gel cartridge, Varian Bond Elut), eluting with 20-60% ethyl acetate in cyclohexane, to give the title compound as a white solid (0.419g).

LC/MS (system A) Rt 2.67min Mass spectrum *m/z* 220 [MH^+].

Intermediate 23: {(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methylamine

Intermediate 23 was made in an analogous manner to that of Intermediate 11

Chiral preparative HPLC retention time 25.2min

Intermediate 24: [(2R,5R)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methylamine (mixture with trans isomer, cis:trans 60:40)

Intermediate 24 was made in an analogous manner to that of Intermediate 31from (2R)-2-aminopropan-1-ol.

LC-MS (System A): Rt 1.9 mins Mass Spectrum *m/z* 289 [MH^+].

Intermediate 25: tert-Butyl 4-{[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}butanoate

4-Aminobutyric acid tert-butyl ester hydrochloride (0.235g) was added to a stirred solution of Intermediate 13 (0.440g) and N,N-diisopropylethylamine (0.42ml) in dry dichloromethane (20ml) under nitrogen, and the mixture was stirred at 22°C for 18h. The mixture was treated with saturated aqueous potassium carbonate (20ml) and stirred for 5 min. The layers were separated and the organic layer applied to a silica gel cartridge (10g Varian Bond Elut). Elution with dichloromethane, ether, ethyl acetate, and acetone gave the crude product (0.357g). Further purification by chromatography on silica gel (10g Varian Bond Elut

cartridge), eluting with dichloromethane (1 column volume), ether (4 column volumes) and ethyl acetate (8 column volumes) gave the title compound as a gum (0.345g).

LC-MS (System A) Rt 2.66min Mass Spectrum *m/z* 460 [MH^+].

Intermediate 26: 4-{[({[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}butanoic acid hydrochloride

Intermediate 25 (0.345g) was dissolved in 4M hydrogen chloride in dioxane (5ml), and the mixture was allowed to stand at 22°C for 19.5h. The solvent was evaporated in vacuo to give the title compound as a white solid (0.330g).

LC-MS (System A) Rt 2.16min Mass Spectrum *m/z* 404 [MH^+].

Intermediate 27: 2-[3-(pyrrolidin-1-ylsulfonyl)propyl]-1H-isoindole-1,3(2H)-dione

A solution of 3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propane-1-sulfonyl chloride (0.288g) in dry tetrahydrofuran (5ml) was treated with N,N-diisopropylethylamine (0.350ml) and pyrrolidine (0.10ml) at 22°C under nitrogen, and the mixture was stirred at 22°C for 1h. After standing overnight at room temperature, the mixture was partitioned between saturated aqueous sodium bicarbonate (10ml) and ethyl acetate (2x10ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated in vacuo to give a white solid (0.145g).

LC-MS (System A) Rt 2.81min. Mass Spectrum *m/z* 323 [MH^+].

Intermediate 28: 3-(Pyrrolidin-1-ylsulfonyl)propylamine

A solution of Intermediate 27 (0.139g) in isopropanol (7.6ml) and water (1.3ml) was treated with sodium borohydride (0.081g), and the mixture was stirred at room temperature under nitrogen for 19h. Glacial acetic acid (0.45ml) was added cautiously and the mixture heated at 80°C for 2h. The solvents were evaporated in vacuo to give a white solid, which was dissolved in methanol and applied to a sulphonic acid ion exchange cartridge (10g Isolute SCX). Elution with methanol followed by 10% 0.880 ammonia in methanol, and evaporation of the ammonia/methanol fraction gave the title compound as a white solid (0.027g).

TLC SiO_2 (dichloromethane:ethanol:0.880 ammonia 89:10:1) Rf 0.2

Intermediate 29: 4-Nitrophenyl [(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate hydrochloride

A mixture of triethylamine (0.101ml) and Intermediate 11 (2.0g) in dichloromethane (20ml) was added dropwise to a solution of 4-nitrophenyl chloroformate (1.62g) in dichloromethane (10ml) with stirring at 0°C under nitrogen. The solution was stirred for 3h at 0°C, allowed to warm to 20°C, and stand for 18h. The volatile components were evaporated in vacuo, and the residue was purified by Biotage flash chromatography on silica gel (90g cartridge),

eluting initially with 10% methanol in dichloromethane and subsequently with 20% methanol in dichloromethane, to give the title compound as a light brown solid (2.5g).
LCMS (System A) R_t 2.89min Mass Spectrum *m/z* 441 [MH^+]

Intermediate 30: 1-(2-Methyl-2H-tetraazol-5-yl)methanamine hydrochloride

To Intermediate 37 (0.47g) was added 4.0M hydrogen chloride in 1,4-dioxane (5ml). The mixture was stirred at 22°C for 3h, and the solvent removed in vacuo. The residue was again dissolved in 4.0M hydrogen chloride in 1,4-dioxane (5ml), and left to stand at 22°C for 18h. Evaporation of the solvent in vacuo gave the title compoundas a cream solid (0.319g).
Thermospray Mass Spectrum *m/z* = 114 [MH^+]

Intermediate 31: 1-[4-(3,4-Dichlorobenzyl)-5-methylmorpholin-2-yl]methanamine (cis/trans ratio 2:1)

A mixture of Intermediate 43 (0.470g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (0.410g) was heated at 80°C under nitrogen for 5h. The mixture was treated with concentrated sulphuric acid (0.6ml) then stirred at 150°C for 42h. The mixture was treated with water (50ml) then washed with ethyl acetate (2x50ml). The dark aqueous phase was basified to ~pH 11 using 5M aqueous sodium hydroxide then extracted with ethyl acetate (2x50ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (0.42g).
LC-MS (System A): Rt 1.74min.

Intermediate 32: tert-Butyl {(2S)-4-[1-(3,4-dichlorophenyl)ethyl]morpholin-2-yl}methylcarbamate

tert-Butyl (2R)-morpholin-2-ylmethylcarbamate (2.00g) in N,N-dimethylformamide (16ml) was treated with N,N-diisopropylethylamine (1.6ml) followed by 4-(1-bromoethyl)-1,2-dichlorobenzene (2.58g). After stirring for five days at room temperature, further portions of 4-(1-bromoethyl)-1,2-dichlorobenzene (2.58g) and N,N-diisopropylethylamine (1.6ml) were added and stirring continued for 24h at room temperature. The solution was treated with dichloromethane (70ml) and saturated aqueous sodium hydrogen carbonate (30ml) and the mixture shaken vigorously. The organic phase was separated and applied equally onto sulphonic acid ion exchange cartridges (5x10g Isolute SCX, pre-treated with methanol). The cartridges were each eluted with methanol (one column volume) followed by 10% 0.880 ammonia in methanol (one column volume); evaporation in vacuo of the combined basic fractions gave the title compound as a clear colourless gum (3.22g)
LC-MS (System A) Rt 2.74min, Mass Spectrum *m/z* 389 [MH^+].

Intermediate 33: 1-{(2S)-4-[1-(3,4-Dichlorophenyl)ethyl]morpholin-2-yl}methanamine dihydrochloride

Intermediate 32 was treated with 4M hydrogen chloride in dioxane (15ml) and the solution stirred for 2h at room temperature. The solution was treated with methanol (20ml) and concentrated in vacuo to give the title compound as an off-white solid (1.53g).

LC/MS (System A) Rt 1.86min and 1.91min, Mass spectrum *m/z* 289 [MH^+].

Intermediates 34 and 35: 4-Nitrophenyl {(2S)-4-[1-(3,4-dichlorophenyl)ethyl]morpholin-2-yl}methylcarbamate (Isomer I and II, respectively)

Intermediate 33 (0.724g) in dichloromethane (5ml) was treated with triethylamine (1.14ml), forming a slurry which was added portion-wise over 5 min to a solution of 4-nitrophenyl chloroformate (0.444g) in anhydrous dichloromethane (5ml) at 0°C under nitrogen. The stirring solution was allowed to warm to room temperature over 2h, then filtered; the filtrate was purified directly by chromatography on silica gel (Biotage 90g column), eluting with 35 – 40% ethyl acetate in cyclohexane, and appropriate fractions evaporated in vacuo to give the title compound (Isomer I) as an opaque yellow film (0.202g).

LC/MS (System A) Rt 2.90min, Mass spectrum *m/z* 454 [MH^+].

Analytical Chiral HPLC Rt 18.03 mins (eluent 25% EtOH/heptane).

Appropriate other fractions were combined and concentrated in vacuo to give the other title compound (Isomer II) (0.196g) as an opaque yellow film.

LC/MS (System A) R_t 2.88min, Mass spectrum *m/z* 454 [MH^+].

Analytical Chiral HPLC Rt 15.38mins (eluent 25% EtOH/heptane).

Intermediate 36: tert-Butyl 1H-tetraazol-5-ylmethylcarbamate

To a stirred solution of 1-(1H-tetraazol-5-yl)methanamine (6.0g) in water (120ml) at 22°C was added sodium hydroxide (4.8g), followed by dropwise addition of a solution of di-tert-butyldicarbonate (13.48g) in methanol (20ml). Further methanol (40ml) was added to the mixture and stirring continued for 4h; the mixture was then allowed to stand for 60h at 4°C. The methanol was evaporated in vacuo and the aqueous residue acidified to approximately pH 6 with 2M aqueous hydrochloric acid. The aqueous mixture was extracted with ethyl acetate (x3) and the combined organic extracts were washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and the solvent evaporated in vacuo to give the title compound as a white solid (1.50g).

Thermospray Mass Spectrum *m/z* 200 [MH^+], 217 [MNH_4^+]

Intermediate 37: tert-Butyl (2-methyl-2H-tetraazol-5-yl)methylcarbamate

To a stirred solution of Intermediate 36 (1.0g) in dichloromethane (35ml) and methanol (10ml) at 22°C under nitrogen was added dropwise 10% trimethylsilyldiazomethane in hexane (12.0ml). The mixture was stirred for 2h at 22°C before acetic acid (2ml) was added dropwise and the solvents were evaporated in vacuo. The crude residue was purified by Biotage flash column chromatography on silica gel (90g cartridge), eluting with 10% cyclohexane in ether. The fractions for the first eluting isomer were combined and the solvents evaporated in vacuo to give the title compound as pale yellow crystals (0.487g).

Thermospray Mass Spectrum *m/z* = 214 [MH^+]

TLC (SiO_2), 10% cyclohexane/ether) R_f = 0.35, visualised with $KMnO_4$

Intermediate 38: tert-Butyl 3-(ethylthio)propylcarbamate

A solution of tert-butyl 3-bromopropylcarbamate (0.30g) in N,N-dimethylformamide (5ml) was treated with ethanethiol (0.104ml) and potassium carbonate (0.29g), and the mixture stirred at room temperature overnight. The mixture was partitioned between water (20ml) and dichloromethane (30ml), and the organic layers evaporated in vacuo to give the title compound (0.236g).

TLC SiO_2 (cyclohexane: ethyl acetate 4:1) Rf 0.5.

Intermediate 39: tert-Butyl 3-(ethylsulfonyl)propylcarbamate

3-Chloroperoxybenzoic acid (0.373g) was added to a stirred solution of Intermediate 38 (0.236g) in dry dichloromethane (6ml) at 22°C under nitrogen, and the mixture was stirred at 22°C for 18h. The mixture was treated with saturated aqueous sodium carbonate (10ml), stirred for 3 min, and the separated organic layer evaporated in vacuo to give the title compound (0.275g).

NMR ($CDCl_3$) 5.15δ(1H, br.t, NH), 3.25δ(2H, q, CH_2), 3.00δ(4H, t+q, 2xCH_2), 2.03δ(2H, m, CH_2), 1.50-1.30δ(12H, s+t, 4xCH_3)

Intermediate 40: 3-(Ethylsulfonyl)propan-1-amine hydrochloride

Intermediate 39 (0.275g) was dissolved in 4M hydrogen chloride in dioxane (3ml), and the solution was allowed to stand at 22°C for 2h. The solvent was evaporated in vacuo to give the title compound as a white solid (186mg).

NMR (D4 MeOH) 3.25δ(2H, t, CH_2), 3.15δ(4H, t+q, 2xCH_2), 2.18δ(2H, m, CH_2), 1.38δ(3H, t, CH_3).

Intermediate 41: [4-(3,4-Dichlorobenzyl)-1,4-oxazepan-2-yl]methylamine

Formyl polystyrene resin (1.6g, loading = 2.95mmol/g) was washed five times with tetrahydrofuran in a glass sintered peptide vessel. A solution of 1-(1,4-oxazepan-2-yl)methanamine (0.619g) in tetrahydrofuran (20ml) was added and the mixture shaken at

22°C for 18h. The mixture was filtered and the resin washed with tetrahydrofuran (4x20ml) and methanol (3x10ml) and dried. A portion of the dried resin (1.2g) was suspended in N,N-dimethylformamide (20ml), N,N-diisopropylethylamine (2.04ml) and 3,4-dichlorobenzylchloride were added. The mixture was stirred gently at 70°C for 22h. After cooling, the mixture was filtered and the resin washed with THF (5x10ml) and dichloromethane (5x10ml) and air-dried on the sinter. The resin was placed into a glass sintered peptide vessel and suspended in tetrahydrofuran (9ml); conc. hydrochloric acid (3ml) was added, and the vessel was shaken for 2h. The resin was filtered off and washed with tetrahydrofuran (2x10ml). The combined filtrates were concentrated in vacuo to give a clear oil, which was applied to an ion exchange cartridge (10g Isolute SCX, pre-conditioned with methanol). Elution with methanol (3 column volumes) followed 10% 0.880 ammonia in methanol (2 column volumes) and evaporation of the basic fractions in vacuo gave a residue. The ion exchange purification was repeated (as above) to give the title compound as a colourless gum (0.256g).

^{1}H NMR ($CDCl_3$): 7.46δ(1H, d, Aromatic CH), 7.38δ(1H, d, Aromatic CH), 7.19δ(1H, dd ,Aromatic CH), 3.94δ(1H, m, CH), 3.80δ(1H, m, CH), 3.59δ(2H, s, CH_2), 3.57δ(1H, m, CH), 2.82-2.53δ(5H, m, 5xCH), 2.38δ(1H, dd, CH), 1.98-1.78δ(2H, m, 2xCH), 1.49δ(2H+H_2O, br.s, NH_2).

Intermediate 42: 2-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-1H-isoindole-1,3(2H)-dione

To a solution of 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (N-(2,3-epoxypropyl)-phthalimide) (2g) in tetrahydrofuran (4 ml) was added 2-[(3,4-dichlorobenzyl)amino]ethanol (2.16 g) with stirring, under a nitrogen atmosphere. The mixture was heated to 66°C for 22h, then cooled to 0°C. A further portion of tetrahydrofuran (10 ml) was added, followed by triphenylphosphine (2.88 g). Diisopropyl azodicarboxylate (2.2 g) was then added over 10 min. The mixture was stirred at 0°C for a further 30 min, and at room temperature for 14h. To the crude solution was added ethyl acetate (100 ml), then 2M aqueous hydrochloric acid (250 ml). The resulting white precipitate was isolated by filtration, and dried in vacuo to give the title compound as its white crystalline hydrochoride salt (2.01g). This was partitioned between 8% aqueous sodium bicarbonate (200ml) and ethyl acetate (50ml). The organic phase was separated, dried over magnesium sulfate and the solvent evaporated in vacuo to give a solid. Dichloromethane (20ml) was added to the residue and the solvent again evaporated in vacuo to give the title compound as a white solid (1.1g).

LC/MS R_t 2.91 min. Mass Spectrum *m/z* 405 [MH^+]

Intermediate 43: 2-[(3,4-Dichlorobenzyl)amino]propan-1-ol

3,4-Dichlorobenzyl chloride (0.988g) was added to 2-amino-1-propanol (4.10g) and the mixture was stirred at 50°C under nitrogen for 2h. The mixture was partitioned between saturated aqueous sodium bicarbonate (100ml) and ethyl acetate (100ml) and the phases were separated. The organic layer was washed with water (4x100ml) and brine, dried (Na_2SO_4) then concentrated under vacuum to give the title compound as a white solid (0.935g).

LC-MS (System A): Rt 2.13min.

Examples

Example 1: N-Benzyl-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

To a stirred solution of Intermediate 3 (0.025g) in dichloromethane (1ml) was added benzylisocyanate (16.8µl). The mixture was stirred at 22°C for 18h before tris-(2-aminoethyl)amine polystyrene (Argonaut Technologies, 0.04g @ 3.85mmol/g) was added. Stirring was continued for a further 72h before the mixture was poured onto a 1g solid phase extraction (Isolute SCX sulphonic acid) cartridge. The cartridge was washed with methanol before eluting with 10% 0.880 ammonia solution in methanol. The basic fraction was evaporated in vacuo to give a pale yellow solid. The solid was purified by eluting through a 1g silica solid phase extraction cartridge (Varian Bondelut) eluting sequentially with dichloromethane, ether, ethyl acetate, acetone, acetonitrile and methanol, to give the title compound as a white solid (0.031g). LC/MS (System A) R_t 2.22 min, Mass Spectrum *m/z* 408 [MH^+].

Example 2: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-methoxybenzyl)urea

Example 2 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-(isocyanatomethyl)-4-methoxybenzene (19.5µl) to give the title compound (0.0257g). LC-MS (System A): Rt 2.23mins, Mass Spectrum *m/z* 438 [MH^+].

Example 3: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-methylbenzyl)urea

Example 3 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-(isocyanatomethyl)-4-methylbenzene (19.1µl) to give the title compound (0.0318g). LC-MS (System A): Rt 2.33mins, Mass Spectrum *m/z* 422 [MH^+].

Example 4: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(3-methylbenzyl)urea

Example 4 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-(isocyanatomethyl)-3-methylbenzene (19.1µl) to give the title compound (0.0382g). LC-MS (System A): Rt 2.32mins, Mass Spectrum *m/z* 422 [MH^+].

Example 5: N-(3-Cyanophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 5 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 3-isocyanatobenzonitrile (0.0196g) to give the title compound (0.0257g). LC-MS (System A): Rt 2.29mins, Mass Spectrum *m/z* 419 [MH$^+$].

Example 6: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-methylbenzyl)urea

Example 6 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-(isocyanatomethyl)-2-methylbenzene (0.0201g) to give the title compound (0.0269g). LC-MS (System A): Rt 2.31mins, Mass Spectrum *m/z* 422 [MH$^+$].

Example 7: N-Cyclohexyl-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 7 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and isocyanatocyclohexane (17.4µl) to give the title compound (0.0298g). LC-MS (System A): Rt 2.26mins, Mass Spectrum *m/z* 400 [MH$^+$].

Example 8: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-phenylethyl)urea

Example 8 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and (2-isocyanatoethyl)benzene (18.9µl) to give the title compound (0.0312g). LC-MS (System A): Rt 2.29mins, Mass Spectrum *m/z* 422 [MH$^+$].

Example 9: N-({4-[2-(2,3-Dihydro-1H-indol-1-yl)-2-oxoethyl]morpholin-2-yl}methyl)-N'-phenylurea

To a stirred solution of Intermediate 7 (0.01g) in N,N-dimethylformamide (0.5ml) was added 1-(2-chloroacetyl)indoline (0.0092g). The mixture was stirred at 22°C for 17h before tris-(2-aminoethyl)amine polystyrene (Argonaut Technologies, 0.01g @ 4.46mmol/g) and polystyrene methyl isocyanate (Argonaut Technologies, 0.033g @ 1.39mmol/g) was added. Stirring was continued for a further 30 min before the mixture was purified by solid phase extraction (1g Isolute SCX sulphonic acid column), eluting with methanol followed by 10% 0.880 ammonia solution in methanol. The basic fraction was evaporated in vacuo to give the title compound as a white solid (0.012g). LC/MS (System A) R_t 2.69 min, Mass Spectrum *m/z* 394 [MH$^+$].

Example 10: N-Allyl-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 10 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 3-isocyanatoprop-1-ene (12.0µl) to give the title compound (0.027g). LC-MS (System A): Rt 1.93mins, Mass Spectrum *m/z* 358 [MH$^+$].

Example 11: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(3-fluorophenyl)urea

Example 11 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-fluoro-3-isocyanatobenzene (15.6µl) to give the title compound (0.019g). LC-MS (System A): Rt 2.35mins, Mass Spectrum *m/z* 412 [MH$^+$].

Example 12: N-(3-Bromophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 12 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-bromo-3-isocyanatobenzene (17.0µl) to give the title compound (0.03g). LC-MS (System A): Rt 2.50mins, Mass Spectrum *m/z* 472 [MH$^+$].

Example 13: N-(3-Chlorophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 13 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-chloro-3-isocyanatobenzene (16.6µl) to give the title compound (0.0247g). LC-MS (System A): Rt 2.46mins, Mass Spectrum *m/z* 428 [MH$^+$].

Example 14: N-(4-Chlorophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 14 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-chloro-4-isocyanatobenzene (17.4µl) to give the title compound (0.0275g). LC-MS (System A): Rt 2.45mins, Mass Spectrum *m/z* 428 [MH$^+$].

Example 15: Methyl 3-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl] amino}benzoate

Example 15 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and methyl 3-isocyanatobenzoate (0.0241g) to give the title compound (0.037g). LC-MS (System A): Rt 2.32mins, Mass Spectrum *m/z* 452 [MH$^+$].

Example 16: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-[4-(difluoromethoxy)phenyl]urea

Example 16 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-(difluoromethoxy)-4-isocyanatobenzene (19.1µl) to give the title compound (0.0252g). LC-MS (System A): Rt 2.41mins, Mass Spectrum *m/z* 460 [MH$^+$].

Example 17: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-fluorophenyl)urea

Example 17 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-fluoro-4-isocyanatobenzene (15.5µl) to give the title compound (0.0311g). LC-MS (System A): Rt 2.30mins, Mass Spectrum *m/z* 421 [MH$^+$].

Example 18: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(methylthio)phenyl]urea

Example 18 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-isocyanato-3-(methylthio)benzene (18.8µl) to give the title compound (0.0352g). LC-MS (System A): Rt 2.41mins, Mass Spectrum *m/z* 440 [MH$^+$].

Example 19: N-(4-Chlorophenyl)-N'-{[4-(1-naphthylmethyl)morpholin-2-yl]methyl}urea

To a stirred solution of Intermediate 9 (0.01g) in N,N-dimethylformamide (1ml) was added1-(chloromethyl)naphthalene (6.1µl). The mixture was stirred at 22°C for 24h before tris-(2-

aminoethyl)amine polystyrene (Argonaut Technologies, 0.01g @ 4.46mmol/g) and polystyrene methyl isocyanate (Argonaut Technologies, 0.033g @ 1.39mmol/g) was added. Stirring was continued for a further 2h before the mixture was purified by solid phase extraction (Isolute SCX sulphonic acid column), eluting with methanol followed by 10% 0.880 ammonia solution in methanol. The basic fraction was evaporated *in vacuo* to give the title compound (0.003g). LC/MS (System A) R_t 2.82 min, Mass Spectrum *m/z* 410 [MH^+].

Example 20: N-(4-Bromophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 20 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-bromo-4-isocyanatobenzene (0.027g) to give the title compound (0.033g). LC-MS (System A): Rt 2.49mins, Mass Spectrum *m/z* 472 [MH^+].

Example 21: N-(4-Chlorophenyl)-N'-{[4-(3-iodobenzyl)morpholin-2-yl]methyl}urea

Example 21 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 1-(bromomethyl)-3-iodobenzene (0.0121g) to give the title compound (0.0087g). LC-MS (System A): Rt 2.83mins, Mass Spectrum *m/z* 486 [MH^+].

Example 22: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(trifluoromethyl)phenyl]urea

Example 22 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-isocyanato-3-(trifluoromethyl)benzene (18.8µl) to give the title compound (0.0112g). LC-MS (System A): Rt 2.56mins, Mass Spectrum *m/z* 462 [MH^+].

Example 23: N-(4-Chlorophenyl)-N'-{[4-(2-naphthylmethyl)morpholin-2-yl]methyl}urea

Example 23 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 2-(bromomethyl)naphthalene (0.009g) to give the title compound (0.0052g). LC-MS (System A): Rt 2.81mins, Mass Spectrum *m/z* 410 [MH^+].

Example 24: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2,6-dichloropyridin-4-yl)urea

Example 24 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 2,6-dichloro-4-isocyanatopyridine (0.0258g) to give the title compound (0.0165g). LC-MS (System A): Rt 2.46mins, Mass Spectrum *m/z* 463 [MH^+].

Example 25: N-(4-Cyanophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 25 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 4-isocyanatobenzonitrile (0.0196g) to give the title compound (0.0325g). LC-MS (System A): Rt 2.29mins, Mass Spectrum *m/z* 419 [MH^+].

Example 26: N-{[4-(3-Chlorobenzyl)morpholin-2-yl]methyl}-N'-(4-chlorophenyl)urea

Example 26 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 1-(bromomethyl)-3-chlorobenzene (5.4µl) to give the title compound (0.0023g). LC-MS (System A): Rt 2.72mins, Mass Spectrum *m/z* 394 [MH$^+$].

Example 27: N-[(4-But-3-enylmorpholin-2-yl)methyl]-N'-(4-chlorophenyl)urea

Example 27 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 4-bromobut-1-ene (4.1µl) to give the title compound(0.0027g). LC-MS (System A): Rt 2.34mins, Mass Spectrum *m/z* 324 [MH$^+$].

Example 28: N-(4-Chlorophenyl)-N'-({4-[2-(phenylthio)ethyl]morpholin-2-yl}methyl)urea

Example 28 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and [(2-bromoethyl)thio]benzene (0.0089g) to give thetitle compound (0.0023g). LC-MS (System A): Rt 2.77mins, Mass Spectrum *m/z* 406 [MH$^+$].

Example 29: N-(4-Chlorophenyl)-N'-{[4-(2-methoxyethyl)morpholin-2-yl]methyl}urea

Example 29 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 1-bromo-2-methoxyethane (3.8µl) to give the title compound (0.0041g). LC-MS (System A) : Rt 2.22mins, Mass Spectrum *m/z* 328 [MH$^+$].

Example 30: N-{[4-(1,1'-Biphenyl-4-ylmethyl)morpholin-2-yl]methyl}-N'-(4-chlorophenyl)urea

Example 30 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 4-(chloromethyl)-1,1'-biphenyl (0.0083g) to give the title compound (0.0052g). LC-MS (System A): Rt 2.95mins, Mass Spectrum *m/z* 436 [MH$^+$].

Example 31: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1-naphthyl)urea

Example 31 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-isocyanatonaphthalene (19.6µl) to give the title compound (0.0304g). LC-MS (System A): Rt 2.43mins, Mass Spectrum *m/z* 444 [MH$^+$].

Example 32: N-(1,1'-Biphenyl-4-yl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 32 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 4-isocyanato-1,1'-biphenyl (0.0266g) to give thetitle compound (0.0314g). LC-MS (System A): Rt 2.65mins, Mass Spectrum *m/z* 470 [MH$^+$].

Example 33: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-phenoxyphenyl)urea

Example 33 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-isocyanato-4-phenoxybenzene (24.6µl) to give the title compound (0.0171g). LC-MS (System A): Rt 2.62mins, Mass Spectrum *m/z* 486 [MH$^+$].

Example 34: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-{4-[(trifluoromethyl)thio]phenyl}urea

Example 34 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-isocyanato-4-[(trifluoromethyl)thio]benzene (21.9µl) to give the title compound (0.0122g). LC-MS (System A): Rt 2.70mins, Mass Spectrum *m/z* 494 [MH$^+$].

Example 35: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-[4-(trifluoromethoxy)phenyl]urea

Example 35 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 1-isocyanato-4-(trifluoromethoxy)benzene (20.6µl) to give the title compound (0.0371g). LC-MS (System A): Rt 2.57mins, Mass Spectrum *m/z* 478 [MH$^+$].

Example 36: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-[4-(dimethylamino)phenyl]urea

Example 36 was prepared in an analogous manner to Example 1 using a mixture of Intermediate 3 (0.025g) and 4-isocyanato-N,N-dimethylaniline (0.0221g) to give the title compound (0.031g). LC-MS (System A): Rt 1.68mins, Mass Spectrum *m/z* 437 [MH$^+$].

Example 37: N-(4-Chlorophenyl)-N'-({4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)urea

Example 37 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 2-chloro-5-(chloromethyl)thiophene (0.0068g) to give the title compound (0.0098g). LC-MS (System A): Rt 2.84mins, Mass Spectrum *m/z* 400 [MH$^+$].

Example 38: N-(4-Chlorophenyl)-N'-{[4-(4-vinylbenzyl)morpholin-2-yl]methyl}urea

Example 38 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 1-(chloromethyl)-4-vinylbenzene (0.0062g) to give the title compound (0.0071g). LC-MS (System A): Rt 2.72mins, Mass Spectrum *m/z* 386 [MH$^+$].

Example 39: 2-{2-[({[(4-Chlorophenyl)amino]carbonyl}amino)methyl]morpholin-4-yl}ethyl benzoate

Example 39 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 2-bromoethyl benzoate (6.5µl) to give the title compound (0.007g). LC-MS (System A): Rt 2.69mins, Mass Spectrum *m/z* 418 [MH$^+$].

Example 40: N-(4-Chlorophenyl)-N'-({4-[2-(4-fluorophenoxy)ethyl]morpholin-2-yl}methyl)urea

Example 40 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 1-(2-bromoethoxy)-4-fluorobenzene (0.0089g) to give the title compound (0.007g). LC-MS (System A): Rt 2.69mins, Mass Spectrum *m/z* 408 [MH$^+$].

Example 41: N-(4-Chlorophenyl)-N'-({4-[4-(4-chlorophenyl)-4-oxobutyl]morpholin-2-yl}methyl)urea

Example 41 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 4-chloro-1-(4-chlorophenyl)butan-1-one (0.0089g) to give the title compound (0.0043g). LC-MS (System A): Rt 2.83mins, Mass Spectrum *m/z* 450 [MH^+].

Example 42: N-(4-Chlorophenyl)-N'-{[4-(3,4-dichlorobenzoyl)morpholin-2-yl]methyl}urea

To a stirred solution of Intermediate 9 (0.05g) was added a solution of 3,4-dichlorobenzoyl chloride (42.7mg) in N,N-dimethylformamide (7ml). The mixture was stirred at 22°C for 15h before the solvent was evaporated in vacuo. The residue was purified by eluting through a 1g silica solid phase extraction cartridge (Varian Bondelut), eluting sequentially with dichloromethane, ether, ethyl acetate, acetone, acetonitrile and methanol, to give the title compound as a white solid (0.080g). LC/MS (System A) R_t 3.10 min, Mass Spectrum *m/z* 442 [MH^+].

Example 43: N'-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N-(4-fluorophenyl)-N-methylurea

4-Fluoro-N-methylaniline (0.007ml) was added to a solution of Intermediate 10 (0.025g) in anhydrous pyridine (1ml). The mixture was heated at 110°C in a thick walled glass vial (Reactivial) for 20h. The mixture was evaporated to remove the pyridine, and partitioned between ethyl acetate (10ml) and saturated aqueous sodium bicarbonate solution (10ml). The organic layer was washed with further sodium bicarbonate (10mlx5), brine (10ml), dried ($MgSO_4$), concentrated in vacuo. The residue was purified by chromatography on silica gel (Trikonex flash tube 2002, 2g), eluting with 70% ethyl acetate in cyclohexane to give the title compound as a pale yellow gum 0.014g. LCMS (system A) R_t 2.52min, Mass Spectrum *m/z* 426 [MH^+].

Example 44: Ethyl {2-[({[(4-chlorophenyl)amino]carbonyl}amino)methyl]morpholin-4-yl}(phenyl)acetate

Example 44 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and ethyl bromo(phenyl)acetate (0.029g) to give the title compound (0.0372g). LC-MS (System A): Rt 3.43mins, Mass Spectrum *m/z* 432 [MH^+].

Example 45: 2-{2-[({[(4-Chlorophenyl)amino]carbonyl}amino)methyl]morpholin-4-yl}-2-phenylacetamide

Example 45 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and 2-bromo-2-phenylacetamide (0.028g) to give the title compound (0.0296g). LC-MS (System A): Rt 2.75mins, Mass Spectrum *m/z* 401 [MH^+].

Example 46: N-(4-Chlorophenyl)-N'-{[4-(cyanomethyl)morpholin-2-yl]methyl}urea

Example 46 was prepared in an analogous manner to Example 19 using a mixture of Intermediate 9 (0.01g) and bromoacetonitrile (2.8µl) to give the title compound(0.0039g). LC-MS (System A): Rt 2.79mins, Mass Spectrum *m/z* 309 [MH$^+$].

Example 47: N-(4-Chlorobenzyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

A suspension of 4-{[(polystyrene resin)methyl]thio}phenyl 4-nitrophenyl carbonate (Prepared as described in Tetrahedron Lett. (1998), 39(22), 3631-3634, 1.5g @ 0.99mmol/g) in N,N-dimethylformamide (15ml) was shaken with Intermediate 3 (0.80g) at 22°C for 1h. The resin was filtered, washed with N,N-dimethylformamide (x2), dichloromethane (x3) and N,N-dimethylformamide. The resin was again shaken with N,N-dimethylformamide (15ml) and Intermediate 3 (0.80g) at 22°C for 1h before being filtered, washed with N,N-dimethylformamide (x2), dichloromethane (x3) and ether (x2) and dried in vacuo to give the intermediate resin 4-{[(polystyrene resin)methyl]thio}phenyl [4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate as orange beads. To a sample of this resin (50mg) in a test tube was added 4-chlorobenzylamine (9.6µl) and 1 drop of 1-methyl-2-pyrrolidinone, and the mixture was placed into a microwave oven and heated at full power (600W) for 5 min. Dichloromethane (2ml) and formylpolystyrene resin were added, and the mixture was shaken at 22°C for 18h. The suspension was poured onto a 1g solid phase extraction (Isolute SCX sulphonic acid) column which was then washed with methanol before eluting with 10% 0.880 ammonia solution in methanol. The basic fraction was evaporated in vacuo to give a cream solid which was further purified by eluting through a 1g silica solid phase extraction cartridge (Varian Bondelut) eluting sequentially with dichloromethane, ether, ethyl acetate, acetone, acetonitrile and methanol, to give the title compound as a white solid (4.7mg). LC/MS (System A) R_t 2.70 min, Mass Spectrum *m/z* 442 [MH$^+$].

Example 48: N-(3-Chlorobenzyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 48 was prepared in an analogous manner to Example 47 using a mixture of Intermediate 3 (0.025g) and 1-(3-chlorophenyl)methanamine (9.6µl) to give the title compound (0.0092g). LC-MS (System A): Rt 2.73mins, Mass Spectrum *m/z* 442 [MH$^+$].

Example 49: N-(2-Chlorobenzyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Example 49 was prepared in an analogous manner to Example 47 using a mixture of Intermediate 3 (0.025g) and 1-(2-chlorophenyl)methanamine (9.6µl) to give the title compound (0.008g). LC-MS (System A): Rt 2.74mins, Mass Spectrum *m/z* 442 [MH$^+$].

Example 50: N-(4-Chlorophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea (ISOMER 1)

Chiral separation from the racemic mixture of Example 14:

Example 14 (racemic mixture, 0.040g) was separated into its single enantiomers of unknown configuration with a chiral preparative HPLC system. The separation was carried out using a Chiralpak AD column (2cm x 25cm), eluting with 60% ethanol in heptane (15ml/min over 25mins, UV detection λ = 215nm) to give the title compound as a white solid (0.012g). Preparative HPLC retention time 7.5min.

Example 51: N-(4-Chlorophenyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea (ISOMER 2)

Example 51 was prepared in an analogous manner to Example 50 yielding the title compound as a white solid (0.012g). Preparative HPLC retention time 11min.

Example 52: N-[3-({[({[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)phenyl]acetamide formate

Example 52 was prepared in an analogous manner to Example 43 from Intermediate 10 (0.04g) and 3-acetamidobenzylamine (0.022g), and purified by Mass Directed Automated Preparative HPLC to yield the title compound (0.008g).

LC-MS (System A) Rt 2.47mins. Mass Spectrum *m/z* 465 [MH^+].

Example 53: 4-({[({[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide

Example 53 was prepared in an analogous manner to Example 47 from Intermediate 3 (0.025g) and 4-aminomethylbenzamide (0.016g) to yield the title compound (0.0083g).

LC-MS (System A) Rt 2.16mins. Mass Spectrum *m/z* 451, 453 [MH^+].

Example 54: 4-({[({[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide

Example 54 was prepared in an analogous manner to Example 43 from Intermediate 13 (0.079g) and 4-aminomethylbenzamide (0.032g) using N,N-dimethylformamide as solvent to yield the title compound (0.0837g).

LC-MS (System A) Rt 2.27mins. Mass Spectrum *m/z* 451, 453 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 41.8min.

Example 55: 4-({[({[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide

Example 55 was prepared in an analogous manner to Example 43 from Intermediate 14 (0.109g) and 4-aminomethylbenzamide (0.045g) using N,N-dimethylformamide as solvent to yield the title compound (0.0828g).

LC-MS (System A) Rt 2.27mins. Mass Spectrum *m/z* 451, 453 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 36.7min.

Example 56: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-prop-2-ynylurea

Example 56 was prepared in an analogous manner to Example 43 from Intermediate 10 (0.040g) and propargylamine (0.006g) using dichloromethane and triethylamine at a temperature of 22°C to yield the title compound (0.028g).

LC-MS (system A) Rt 2.22mins. Mass Spectrum *m/z* 356 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 12.25min and 14.1min.

Example 57: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-prop-2-ynylurea

Example 57 was prepared in an analogous manner to Example 43 from Intermediate 13 (0.1g) and propargylamine (0.014g) using dichloromethane and triethylamine at a temperature of 22°C to yield the title compound (0.064g).

LC-MS (System A) Rt 2.40mins. Mass Spectrum *m/z* 356 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 14.14min.

Example 58: N-{[(2R)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-prop-2-ynylurea

Example 58 was prepared in an analogous manner to Example 43 from Intermediate 14 (0.12g) and propargylamine (0.014g) using dichloromethane and triethylamine at a temperature of 22°C to yield the title compound (0.057g).

LC-MS (System A) Rt 2.37mins. Mass Spectrum *m/z* 356 [MH^+].

Chiral analytical HPLC, eluent 15% EtOH/n-heptane: Rt 12.26min.

Examples 59-122

	Name	Preparation analogous to	Characterising Data
59	N-benzyl-N'-{[(2R,5S)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}urea	Example 1	LC-MS (System A): Rt 2.89 mins. Mass Spectrum *m/z* 422 [MH^+].
60	N-benzyl-N'-{[(2S,5R)-4-(3,4-dichlorobenzyl)-5-methylmorpholin-2-yl]methyl}urea	Example 1	LC-MS (System A): Rt 2.68mins. Mass Spectrum *m/z* 422 [MH^+].

			Normal phase Analytical HPLC Rt 14.2mins.
61	4-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzenesulfonamide	Example 47	LC-MS (System A): Rt 2.40mins. Mass Spectrum *m/z* 487 [MH^+].
62	N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N-methyl-N-pyridin-4-ylurea	Example 43	LC-MS (System A): Rt 2.06mins. Mass Spectrum *m/z* 409 [MH^+].
63	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-methoxybenzyl)urea	Example 50	LC-MS (System A): Rt 2.68mins. Chiral preparative HPLC, eluent 20% ethanol/n-heptane, Rt 18.7min.
64	N,N'-bis{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 43	LC-MS (System A): Rt 2.79mins. Mass Spectrum *m/z* 576 [MH^+].
65	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(3,4-dimethoxybenzyl)urea	Example 47	LC-MS (System A): Rt 2.42mins. Mass Spectrum *m/z* 468, 470 [MH^+].
66	N-(3-cyanobenzyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 47	LC-MS (System A): Rt 2.48mins. Mass Spectrum *m/z* 433, 435 [MH^+].
67	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(pyridin-3-ylmethyl)urea	Example 47	LC-MS (System A): Rt 1.88mins. Mass Spectrum *m/z* 409, 411 [MH^+].
68	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(3-	Example 47	LC-MS (System A): Rt 2.54mins. Mass Spectrum *m/z* 438,

	methoxybenzyl)urea		440 [MH+].
69	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(trifluoromethoxy)benzyl]urea	Example 47	LC-MS (System A): Rt 2.88mins. Mass Spectrum *m/z* 492, 494 [MH+].
70	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[4-(trifluoromethyl)benzyl]urea	Example 47	LC-MS (System A): Rt 2.83mins. Mass Spectrum *m/z* 476, 478 [MH+].
71	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[4-(1,2,3-thiadiazol-4-yl)benzyl]urea	Example 47	LC-MS (System A): Rt 2.59mins. Mass Spectrum *m/z* 492, 494 [MH+].
72	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[4-(trifluoromethoxy)benzyl]urea	Example 47	LC-MS (System A): Rt 2.88mins. Mass Spectrum *m/z* 492, 494 [MH+].
73	N-(3,5-dichlorobenzyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 47	LC-MS (System A): Rt 2.92mins. Mass Spectrum *m/z* 476, 478, 480 [MH+].
74	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(trifluoromethyl)benzyl]urea	Example 47	LC-MS (System A): Rt 2.82mins. Mass Spectrum *m/z* 476, 478 [MH+].
75	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2,4-difluorobenzyl)urea	Example 136	LC-MS (System A): Rt 2.88mins. Mass Spectrum *m/z* 444, 446 [MH+].
76	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(3,4-difluorobenzyl)urea	Example 47	LC-MS (System A): Rt 2.65mins. Mass Spectrum *m/z* 444, 446 [MH+].
77	N-{[4-(3,4-	Example 47	LC-MS (System A):

	dichlorobenzyl)morpholin-2-yl]methyl}-N'-(3-fluorobenzyl)urea		Rt 2.58mins. Mass Spectrum *m/z* 426, 428 [MH$^+$].
78	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-indol-5-ylmethyl)urea	Example 47	LC-MS (System A): Rt 2.51mins. Mass Spectrum *m/z* 447, 449 [MH$^+$].
79	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-indol-4-ylmethyl)urea	Example 47	LC-MS (System A): Rt 2.50mins. Mass Spectrum *m/z* 447, 449 [MH$^+$].
80	N-(3,4-dichlorobenzyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 47	LC-MS (System A): Rt 2.89mins. Mass Spectrum *m/z* 476, 478, 480 [MH$^+$].
81	3-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N-methylbenzamide	Example 131	LC-MS (System A): Rt 2.29mins. Mass Spectrum *m/z* 465, 467 [MH$^+$].
82	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2,3-dihydro-1-benzofuran-5-ylmethyl)urea	Example 136	LC-MS (System A): Rt 2.77mins. Mass Spectrum *m/z* 450, 452 [MH$^+$].
83	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(5-methylisoxazol-3-yl)methyl]urea	Example 47	LC-MS (System A): Rt 2.27mins. Mass Spectrum *m/z* 413, 415 [MH$^+$].
84	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[2-(trifluoromethoxy)benzyl]urea	Example 47	LC-MS (System A): Rt 2.82mins. Mass Spectrum *m/z* 492, 494 [MH$^+$].
85	methyl 3-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}	Example 47	LC-MS (System A): Rt 2.55mins. Mass Spectrum *m/z* 466,

	methyl)benzoate		468 [MH$^+$].
86	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[2-(trifluoromethyl)benzyl]urea	Example 47	LC-MS (System A): Rt 2.78mins. Mass Spectrum *m/z* 476, 478 [MH$^+$].
87	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-fluorobenzyl)urea	Example 47	LC-MS (System A): Rt 2.58mins. Mass Spectrum *m/z* 426, 428 [MH$^+$].
88	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-fluorobenzyl)urea	Example 47	LC-MS (System A): Rt 2.55mins. Mass Spectrum *m/z* 426, 428 [MH$^+$].
89	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-isopropoxybenzyl)urea	Example 47	LC-MS (System A): Rt 2.73mins. Mass Spectrum *m/z* 466, 468 [MH$^+$].
90	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2,4-dimethoxybenzyl)urea	Example 47	LC-MS (System A): Rt 2.59mins. Mass Spectrum *m/z* 468, 470 [MH$^+$].
91	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[2-(4-methoxyphenyl)ethyl]urea	Example 47	LC-MS (System A): Rt 2.60mins. Mass Spectrum *m/z* 452, 454 [MH$^+$].
92	N-[2-(4-tert-butoxyphenyl)ethyl]-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 47	LC-MS (System A): Rt 2.84mins. Mass Spectrum *m/z* 494, 496 [MH$^+$].
93	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(thien-2-ylmethyl)urea	Example 43	LC-MS (System A): Rt 2.58mins. Mass Spectrum *m/z* 414 [MH$^+$].
94	N-{[4-(3,4-	Example 47	LC-MS (System A):

	dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-thien-2-ylethyl)urea		Rt 2.54mins. Mass Spectrum *m/z* 428, 430 [MH$^+$].
95	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(dimethylamino)benzyl]urea	Example 47	LC-MS (System A): Rt 2.26mins. Mass Spectrum *m/z* 451, 453 [MH$^+$].
96	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-propylurea	Example 47	LC-MS (System A): Rt 2.26mins. Mass Spectrum *m/z* 360, 362 [MH$^+$].
97	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[2-(methylthio)benzyl]urea	Example 47	LC-MS (System A): Rt 2.67mins. Mass Spectrum *m/z* 454, 456 [MH$^+$].
98	N-(4-cyanobenzyl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 47	LC-MS (System A): Rt 2.47mins. Mass Spectrum *m/z* 433, 435 [MH$^+$].
99	2-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}-N-methylethanesulfonamide	Example 43	LC-MS (System A): Rt 2.35mins. Mass Spectrum *m/z* 438 [MH$^+$].
100	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(4-hydroxybut-2-ynyl)urea	Example 43	LC-MS (System A): Rt 2.14mins. Mass Spectrum *m/z* 386 [MH$^+$].
101	N-allyl-N'-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 50	LC-MS (System A): Rt 2.40mins. Chiral preparative HPLC, eluent 20% ethanol/n-heptane, Rt 9.3min.
102	N-but-3-enyl-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-	Example 43	LC-MS (System A): Rt 2.40mins.

	yl]methyl}urea		Mass Spectrum *m/z* 372 [MH$^+$].
103	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[2-(pyrrolidin-1-ylsulfonyl)ethyl]urea	Example 43	LC-MS (System A): Rt 2.19mins. Mass Spectrum *m/z* 479 [MH$^+$].
104	N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N-(4-methoxybenzyl)-N-methylurea	Example 43	LC-MS (System A): Rt 2.81mins. Mass Spectrum *m/z* 452 [MH$^+$].
105	methyl 4-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzoate	Example 136	LC-MS (System A): Rt 2.65mins. Mass Spectrum *m/z* 466 [MH$^+$].
106	4-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N-(1,3-thiazol-2-yl)benzenesulfonamide	Example 136	LC-MS (System A): Rt 2.61mins. Mass Spectrum *m/z* 570, 572 [MH$^+$].
107	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-({5-[(dimethylamino)methyl]-2-furyl}methyl)urea	Example 136	LC-MS (System A): Rt 1.95mins. Mass Spectrum *m/z* 455, 457 [MH$^+$].
108	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(3-methoxyisothiazol-5-yl)methyl]urea	Example 136	LC-MS (System A): Rt 2.52mins. Mass Spectrum *m/z* 445, 447 [MH$^+$].
109	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(4-methyl-1,3-thiazol-2-yl)methyl]urea	Example 136	LC-MS (System A): Rt 2.35mins. Mass Spectrum *m/z* 429, 431 [MH$^+$].
110	N-{[4-(3,4-dichlorobenzyl)morpholin-2-	Example 136	LC-MS (System A): Rt 2.40mins.

	yl]methyl}-N'-[(6-methoxypyridin-3-yl)methyl]urea		Mass Spectrum *m/z* 439, 441 [MH$^+$].
111	5-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)nicotinamide	Example 136	LC-MS (System A): Rt 2.10mins. Mass Spectrum *m/z* 452, 454 [MH$^+$].
112	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(pyrazin-2-ylmethyl)urea	Example 136	LC-MS (System A): Rt 2.14mins. Mass Spectrum *m/z* 410, 412 [MH$^+$].
113	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)urea	Example 136	LC-MS (System A): Rt 2.26mins. Mass Spectrum *m/z* 415, 417 [MH$^+$].
114	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-1,3-thiazol-4-yl)methyl]urea	Example 136	LC-MS (System A): Rt 2.34mins. Mass Spectrum *m/z* 429, 431 [MH$^+$].
115	methyl 2-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-4-methyl-1,3-thiazole-5-carboxylate	Example 136	LC-MS (System A): Rt 2.49mins. Mass Spectrum *m/z* 487, 489 [MH$^+$].
116	N-[(5-amino-1-phenyl-1H-pyrazol-4-yl)methyl]-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 136	LC-MS (System A): Rt 2.45mins. Mass Spectrum *m/z* 489, 491 [MH$^+$].
117	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)urea	Example 136	LC-MS (System A): Rt 2.26mins. Mass Spectrum *m/z* 448, 450 [MH$^+$].
118	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-({5-	Example 136	LC-MS (System A): Rt 1.98mins. Mass Spectrum *m/z* 471,

	[(dimethylamino)methyl]thien-2-yl}methyl)urea		473 [MH$^+$].
119	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-furylmethyl)urea	Example 136	LC-MS (System A): Rt 2.42mins. Mass Spectrum *m/z* 398, 400 [MH$^+$].
120	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-2H-tetraazol-5-yl)methyl]urea	Example 136	LC-MS (System A): Rt 2.21mins. Mass Spectrum *m/z* 414, 416 [MH$^+$]. Chiral analytical HPLC, eluent 30% EtOH/n-heptane(0.1%TFA), Rt 9.99min and 12.75min.
121	N-but-3-ynyl-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 43	LC-MS (System A): Rt 2.32mins. Mass Spectrum *m/z* 370 [MH$^+$].
122	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(phenylsulfonyl)propyl]urea	Example 43	LC-MS (System A): Rt 2.46mins. Mass Spectrum *m/z* 500 [MH$^+$].

Example 123: 4-({[({[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzoic acid compound with N,N,N-triethylamine (1:1)

Sodium hydroxide (0.09g) was added to a stirred solution of Example 105 (0.522g) in a mixture of water (5ml) and methanol (5ml) at 20°C, and stirring was continued at 20°C for 18h. The pH of the mixture was adjusted to approximately 6 by the addition of 2M aqueous sodium hydroxide and the mixture was applied in two equal portions to ion exchange cartridges (10g Isolute SCX pre-conditioned with methanol). Elution with methanol (3 column volumes) followed 10% triethylamine in methanol (2 column volumes) and evaporation of the first basic fractions in vacuo gave the title compound as a tan solid (0.468g).

LCMS (System A) R_t 2.60min Mass Spectrum *m/z* 452 [MH$^+$]

Example 124: 4-({[({[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide hydrochloride

4.0M hydrogen chloride in 1,4-dioxane (2.0ml) was added to a stirred solution of Example 54 (0.100g) in methanol (10ml), and stirring was continued at 22°C for 1h. The solvents were evaporated under a stream of nitrogen and the residue re-dissolved in methanol (4ml). Toluene (4ml) was added, and the solvents were again evaporated under a stream of nitrogen. The residue was re-dissolved in methanol (4ml), toluene (4ml) added, and the solvents again evaporated under a stream of nitrogen. The white residue was triturated in ether and the solvent evaporated under a stream of nitrogen before being dried in vacuo to give the title compound as a white solid (0.117g).

LCMS (System A) R_t 2.25min Mass Spectrum *m/z* 451 [MH^+]

^{1}H NMR (D6 DMSO): 11.45δ(1H, br.s, NH^+), 7.97-7.92δ(2H, d+br.s, Aromatic CH+NH) 7.82δ(2H, ½AA'BB', 2xAromatic CH), 7.75δ(1H, d, Aromatic CH), 7.59δ(1H, dd, Aromatic CH), 7.32δ(1H, br.s, NH), 7.28δ(2H, ½AA'BB', 2xAromatic CH), 6.62, 6.28δ(2H, 2xv.br.s, $CONH_2$), 4.35δ(2H, AB, CH_2), 4.25δ(2H, s, CH_2), 3.95δ(1H, dd, CH), 3.88-3.79δ(2H, m, 2xCH), 3.28δ(1H, br.d, CH), 3.25-3.18δ(2H, br.m, 2xCH), 3.09δ(1H, dd, CH), 3.00δ(1H, br.m, CH), 2.78δ(1H, m, CH)

Example 125: N-{[(2S)-4-(2,3-dichlorobenzyl)morpholin-2-yl]methyl}-N'-prop-2-ynylurea

A solution of Intermediate 22 (0.024g) in dichloromethane (1ml) was stirred with Intermediate 20 (0.033g) and N,N-diisopropylethylamine (0.022ml) for 3h at 23°C. The solvent was removed in vacuo and the residue was purified by solid phase extraction (Isolute SCX sulphonic acid column) eluting with methanol followed by 10% 0.880 ammonia solution in methanol. The basic fraction was concentrated in vacuo, and the residue was dissolved in dichloromethane (5ml), and the solution shaken with polystyrene methyl isocyanate resin (Argonaut technologies, 0.256g, 1.43mmol/g) for 16h. The solution was drained from the resin and the resin washed with dichloromethane (8ml); the combined filtrate and washings were concentrated in vacuo to give the title compound as a pale yellow gum (0.02g).

LC/MS (System A) Rt 2.17min, Mass spectrum *m/z* 356 [MH^+].

Example 126: N-({(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methyl)-N'-prop-2-ynylurea

Example 126 was prepared in an analogous manner to Example 125 from Intermediate 23, (0.030g). Further purification using a silica gel solid phase extraction cartridge (1g Varian Bond Elut), eluting with 0-5% methanol in ethyl acetate, gave the title compound as a clear gum (0.025g).

LC/MS (System A) Rt 1.95 min Mass spectrum *m/z* 328 [MH$^+$].

Example 127: N-{[(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methyl}-N'-prop-2-ynylurea

Example 127 was prepared in an analogous manner to Example 125 from Intermediate 19 (0.029g). Further purification using a silica gel solid phase extraction cartridge (1g Varian Bond Elut), eluting with 0-5% methanol in ethyl acetate, gave the title compound as a clear gum (0.021g).

LC/MS (System A) Rt 1.93min Mass spectrum *m/z* 322 [MH$^+$].

Examples 128-130

	Name	Preparation analogous to	Characterising Data
128	3-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N,N-dimethylbenzamide	Example 131	LC-MS (System A): Rt 2.32mins. Mass Spectrum *m/z* 479, 481 [MH$^+$].
129	3-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N-ethylbenzamide	Example 131	LC-MS (System A): Rt 2.33mins. Mass Spectrum *m/z* 479, 481 [MH$^+$].
130	N-cyclopropyl-3-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide	Example 131	LC-MS (System A): Rt 2.34mins. Mass Spectrum *m/z* 491, 493 [MH$^+$].

Example 131: 4-({[({[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N-methylbenzamide

Example 123 (0.050g), 1-hydroxybenzotriazole (0.066g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.116g) were stirred in N,N-dimethylformamide (4.2ml) and N,N-diisopropylethylamine (0.132ml) was added to the mixture. Stirring was continued at 20°C until a clear solution was obtained. 2.0M methylamine in tetrahydrofuran (0.379ml) was added to a portion of the mixture (1.0ml) and the mixture was stirred at 20°C under nitrogen for 17h. The mixture was applied in two equal portions to ion exchange cartridges (2x 2g Isolute SCX pre-conditioned with methanol). Elution with methanol (3 column volumes) followed by 10% 0.880 ammonia in methanol (2 column volumes) and evaporation of the basic fractions in vacuo gave the crude product. Purification by Biotage flash chromatography on a silica gel cartridge (8g), eluting with 100:8:1

dichloromethane/ethanol/0.880 ammonia, gave the title compound as a white solid (0.0124g).

LCMS (System A) R_t 2.22min, Mass Spectrum *m/z* 465 [MH^+].

Chiral analytical HPLC, eluent 15% ethanol in n-heptane, Rt 24.0min and 27.7min.

Examples 132-135

	Name	Preparation analogous to	Characterising Data
132	4-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N,N-dimethylbenzamide	Example 131	LC-MS (System A): Rt 2.30mins. Mass Spectrum *m/z* 479, 481 [MH^+].
133	4-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N-ethylbenzamide	Example 131	LC-MS (System A): Rt 2.28mins. Mass Spectrum *m/z* 479, 481 [MH^+].
134	N-cyclopropyl-4-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide	Example 131	LC-MS (System A): Rt 2.26mins. Mass Spectrum *m/z* 491, 493 [MH^+].
135	N-{[3-(4-chlorophenyl)isoxazol-5-yl]methyl}-N'-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 136	LC-MS (System A): Rt 2.98mins. Mass Spectrum *m/z* 509, 511 [MH^+].

Example 136: N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-2H-tetraazol-5-yl)methyl]urea

Intermediate 30 (0.041g) was added to a stirred solution of Intermediate 29(0.110g) in N,N-dimethylformamide (2ml) at 22°C, and N,N-diisopropylethylamine (0.052ml) was added. After stirring for 20 h, the mixture was applied in two equal portions to ion exchange cartridges (10g Isolute SCX pre conditioned with methanol). Elution with methanol (3 column volumes) followed by 10% 0.880 ammonia in methanol (2 column volumes) and evaporation of the first basic fractions in vacuo gave the crude product. Purification by Biotage flash chromatography on silica gel (8g cartridge), eluting with 100:8:1 dichloromethane/ethanol/0.880 ammonia, gave the title compound as a white solid, (0.0828g).

LC/MS (System A) Rt 2.19min Mass Spectrum *m/z* 414 [MH$^+$].

Chiral analytical HPLC, eluent 30% ethanol/ 0.1% trifluoroacetic acid in n-heptane, Rt 10.1min.

Examples 137-144

	Name	Preparation analogous to	Characterising Data
137	4-(2-{[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}ethyl)benzenesulfonamide	Example 136	LC-MS (System A): Rt 2.38mins. Mass Spectrum *m/z* 501, 503 [MH$^+$].
138	3-({[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N-methylbenzamide	Example 136	LC-MS (System A): Rt 2.28mins. Mass Spectrum *m/z* 465, 467 [MH$^+$].
139	N-cyclopropyl-3-({[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzenesulfonamide	Example 136	LC-MS (System A): Rt 2.57mins. Mass Spectrum *m/z* 527, 529 [MH$^+$].
140	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(4-methyl-1,3-thiazol-2-yl)methyl]urea	Example 136	LC-MS (System A): Rt 2.33mins. Mass Spectrum *m/z* 429, 431 [MH$^+$].
141	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)urea	Example 136	LC-MS (System A): Rt 2.23mins. Mass Spectrum *m/z* 415, 417 [MH$^+$].
142	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-{[3-(4-methoxyphenyl)isoxazol-5-yl]methyl}urea	Example 136	LC-MS (System A): Rt 2.73mins. Mass Spectrum *m/z* 505, 507 [MH$^+$].
143	tert-butyl 4-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}	Example 43	LC-MS (System A): Rt 2.69 mins. Mass Spectrum *m/z* 515

	methyl)piperidine-1-carboxylate		[MH$^+$].
144	N-cyclopropyl-4-({[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzenesulfonamide	Example 136	LC-MS (System A): Rt 2.54mins. Mass Spectrum *m/z* 527, 529 [MH$^+$].

Example 145: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(ethylsulfonyl)propyl]urea

Intermediate 40 (0.0225g) and N,N-diisopropylethylamine (0.021ml) were added to a solution of Intermediate 10 (0.044g) in dichloromethane (3ml), and the mixture was shaken at 22°C for 19h. Formyl polystyrene scavenging resin (2.95mmol/g, 0.02g) was added and the mixture shaken for 2h. The mixture was filtered, the resin washed with dichloromethane, and the filtrate applied directly to a sulphonic acid ion exchange cartridge (2g Isolute SCX). Elution with methanol followed by 10% 0.880 ammonia in methanol gave the crude product (0.04g). Purification by chromatography on silica gel (Varian Bond Elut 1g cartridge), eluting with dichloromethane, ether, ethyl acetate, and acetone, gave the title compound (0.029mg). LC-MS (System A) Rt 2.22mins Mass Spectrum *m/z* 452 [MH$^+$].

Examples 146-159

	Name	Preparation analogous to	Characterising Data
146	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(isopropylsulfonyl)propyl]urea	Example 145	LC-MS (System A): Rt 2.30mins. Mass Spectrum *m/z* 466 [MH$^+$].
147	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(propylsulfonyl)propyl]urea	Example 145	LC-MS (System A): Rt 2.34mins. Mass Spectrum *m/z* 466 [MH$^+$].
148	N-[3-(tert-butylsulfonyl)propyl]-N'-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea	Example 145	LC-MS (System A): Rt 2.41mins. Mass Spectrum *m/z* 480 [MH$^+$].
149	4-({[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}	Example 57	LC-MS (System A): Rt 2.28mins. Mass Spectrum *m/z* 465

	methyl)-N-methylbenzamide		[MH+]. Chiral analytical HPLC, eluent 15% ethanol in n-heptane, detection at 230nm, Rt 29.7min.
150	N-cyclopropyl-4-({[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide	Example 57	LC-MS (System A): Rt 2.38mins. Mass Spectrum *m/z* 491 [MH+].
151	ethyl 4-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}piperidine-1-carboxylate	Example 47	LC-MS (System A): Rt 2.61mins. Mass Spectrum *m/z* 473 [MH+].
152	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[2-(2-oxoimidazolidin-1-yl)ethyl]urea	Example 47	LC-MS (System A): Rt 2.05 mins. Mass Spectrum *m/z* 430, 432 [MH+].
153	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-tetrahydro-2H-pyran-4-ylurea	Example 47	LC-MS (System A): Rt 2.42mins. Mass Spectrum *m/z* 358[MH+].
154	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-morpholin-4-ylethyl)urea	Example 47	LC-MS (System A): Rt 1.76mins. Mass Spectrum *m/z* 431 [MH+].
155	ethyl 4-[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]piperazine-1-carboxylate	Example 47	LC-MS (System A): Rt 2.36mins. Mass Spectrum *m/z* 459 [MH+].
156	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}morpholine-4-carboxamide	Example 47	LC-MS (System A): Rt 2.12mins. Mass Spectrum *m/z* 388 [MH+].
157	N-{[4-(3,4-	Example 47	LC-MS (System A):

	dichlorobenzyl)morpholin-2-yl]methyl}-4-(3-fluorophenyl)piperazine-1-carboxamide		Rt 2.77mins. Mass Spectrum *m/z* 481 [MH$^+$].
158	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-4-methylpiperidine-1-carboxamide	Example 47	LC-MS (System A): Rt 2.56mins. Mass Spectrum *m/z* 400 [MH$^+$].
159	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-4-(2-furoyl)piperazine-1-carboxamide	Example 47	LC-MS (System A): Rt 2.31mins. Mass Spectrum *m/z* 481 [MH$^+$].

Example 160: N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[1-(methylsulfonyl)piperidin-4-yl]urea

Methane sulphonyl chloride (0.009ml) was added to a solution of Intermediate 16 (0.04g) and N,N-diisopropylethylamine (0.048ml) in dichloromethane (3ml). The solution was stirred for 5h at 23°C. The solvent was removed in vacuo and the residue was purified by solid phase extraction (Isolute SCX sulphonic acid column) eluting with methanol followed by 10% 0.880 ammonia solution in methanol, to give the title compound as a pale yellow gum (0.034g).

LC/MS (System A) Rt 2.5min Mass spectrum *m/z* 479 [MH$^+$].

Example 161: N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-{1-[(3,5-dimethylisoxazol-4-yl)sulfonyl]piperidin-4-yl}urea

Example 161 was made in an analogous manner to that of Example 160

LC-MS (System A) Rt 2.86mins. Mass Spectrum *m/z* 561 [MH$^+$].

Example 162: N-(1-benzoylpiperidin-4-yl)-N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Benzoyl choride (0.014ml) was added to a solution of Intermediate 16 (0.04g) and N,N-diisopropylethylamine (0.048ml) in dichloromethane (3ml). The solution was stirred for 5h at 23°C. The solvent was removed in vacuo and the residue purified by solid phase extraction (Isolute SCX sulphonic acid column) eluting with methanol followed by 10% 0.880 ammonia solution in methanol. The basic fraction was concentrated in vacuo and the residue was further purified using a silica gel solid phase extraction cartridge (1g Varian Bond Elut),

eluting sequentially with dichloromethane, ethyl acetate, acetone, acetonitrile, and methanol, to give the title compound as a clear gum (0.024g).

LC/MS (System A) Rt 2.63min, Mass spectrum *m/z* 506 [MH^+].

Examples 163-168

	Name	Preparation analogous to	Characterising Data
163	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[4-(methylsulfonyl)benzyl]urea	Example 47	LC-MS (System A): Rt mins 2.61. Mass Spectrum *m/z* 486 [MH^+].
164	N'-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N-(3-hydroxypropyl)-N-pyridin-2-ylurea	Example 43	LC-MS (System A): Rt 2.19mins. Mass Spectrum *m/z* 453 [MH^+].
165	N-(2-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}ethyl)methanesulfonamide	Example 43	LC-MS (System A): Rt 2.33mins. Mass Spectrum *m/z* 439 [MH^+].
166	4-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}butanamide	Example 43	LC-MS (System A): Rt 2.21mins. Mass Spectrum *m/z* 403 [MH^+].
167	(2E)-4-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}but-2-enoic acid compound with N,N,N-triethylamine (1:1)	Example 43	LC-MS (System A): Rt 2.18mins. Mass Spectrum *m/z* 402 [MH^+].
168	N-(2-{[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}ethyl)acetamide	Example 43	LC-MS (System A): Rt 2.06mins. Mass Spectrum *m/z* 403 [MH^+].

Example 169: N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}thiomorpholine-4-carboxamide

1,4-Thioxane (0.02g) and N,N-diisopropylethylamine (0.04ml) were added to a solution of Intermediate 10 (0.08g) in dichloromethane (2ml). The mixture was stirred at 23°C for 16h, and the solvent evaporated in vacuo. The residue was dissolved in dichloromethane (3ml), and the solution shaken with polystyrene methyl isocyanate resin (Argonaut Technologies, 0.14g, 1.45mmol/g) for 2h. The solution was drained from the resin, and the resin washed with dichloromethane (6ml) and methanol (3ml); the combined filtrate and washings were concentrated in vacuo. The residue was purified further by solid phase extraction (Isolute SCX sulphonic acid column), eluting with methanol followed by 10% 0.880 ammonia solution in methanol, to give the title compound as a pale yellow gum (0.065g).

LCMS (system A) R_t 2.55min, Mass Spectrum *m/z* 404 [MH^+].

Examples 170-174

	Name	Preparation analogous to	Characterising Data
170	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,1-dioxidotetrahydrothien-3-yl)urea	Example 43	LC-MS (System A): Rt 2.35mins. Mass Spectrum *m/z* 436 [MH^+].
171	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-tetrahydro-2H-thiopyran-4-ylurea	Example 43	LC-MS (System A): Rt 2.65mins. Mass Spectrum *m/z* 418 [MH^+].
172	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[1-(4-fluorophenyl)ethyl]urea	Example 136	LC-MS (System A): Rt 2.89 mins. Mass Spectrum *m/z* 440, 442 [MH^+].
173	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1-methyl-1-phenylethyl)urea	Example 136	LC-MS (System A): Rt 2.96 mins. Mass Spectrum *m/z* 436, 438 [MH^+].
174	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-thioxo-2,3-dihydro-1H-imidazol-4-yl)methyl]urea	Example 136	LC-MS (System A): Rt 2.10 mins. Mass Spectrum *m/z* 430, 432 [MH^+].

Example 175: N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}thiomorpholine-4-carboxamide 1,1-dioxide

Oxone (0.135g) was added to Example 169 (0.06g) in methanol:water (10:1, 4ml) at 23°C under nitrogen, and the mixture was stirred for 18h. The methanol was removed in vacuo, the aqueous layer was diluted with sodium sulphite solution (5%, 5ml) and the product was extracted into dichloromethane (8ml). The organic layer was washed with brine (5ml), dried ($MgSO_4$) and concentrated in vacuo to give the title compound as a white solid (0.055g). LC/MS (System A) Rt 2.34min Mass spectrum *m/z* 436 [MH^+].

Examples 176-181

	Name	Preparation analogous to	Characterising Data
176	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-4-(methylsulfonyl)piperazine-1-carboxamide	Example 43	LC-MS (System A): Rt 2.24mins. Mass Spectrum *m/z* 465 [MH^+].
177	N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-2-(4-methylpyridin-2-yl)pyrrolidine-1-carboxamide	Example 136	LC-MS (System A): Rt 2.19 mins. Mass Spectrum *m/z* 463, 465 [MH^+].
178	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[2-(4-methoxyphenyl)-2-oxoethyl]urea	Example 136	LC-MS (System A): Rt 2.55 mins. Mass Spectrum *m/z* 466, 468 [MH^+].
179	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxamide	Example 136	LC-MS (System A): Rt 2.69 mins. Mass Spectrum *m/z* 448, 450 [MH^+].
180	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-phenoxyurea	Example 136	LC-MS (System A): Rt 2.57 mins. Mass Spectrum *m/z* 410, 412 [MH^+].
181	N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-	Example 136	LC-MS (System A): Rt 2.64 mins.

	yl]methyl}-N'-(2-phenoxyethyl)urea		Mass Spectrum *m/z* 438, 440 [MH$^+$].

Example 182: N-{[1-(Cyclopropylcarbonyl)piperidin-4-yl]methyl}-N'-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea

Cyclopropanecarbonyl chloride (0.014ml) was added to a solution of Intermediate 18 (0.54g) and N,N-diisopropylethylamine (0.063ml) in dichloromethane (2ml). The solution was stirred for 3h at 23°C. The solvent was removed in vacuo and the residue purified by solid phase extraction (Isolute SCX sulphonic acid column) eluting with methanol followed by 10% 0.880 ammonia solution in methanol. The basic fraction was concentrated in vacuo and the residue was further purified using a silica gel solid phase extraction cartridge (1g Varian Bond Elut) eluting with 0-1% methanol in ethyl acetate, to give the title compound as a clear gum (0.023g).

LC/MS (system A) Rt 2.35min Mass spectrum *m/z* 483 [MH$^+$].

Example 183: N-{[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-N'-{[1-(methylsulfonyl)piperidin-4-yl]methyl}urea

Methane sulphonyl choride (0.013ml) was added to a solution of Intermediate 18 (0.054g) and N,N-diisopropylethylamine (0.063ml) in dichloromethane (2ml). The solution was stirred for 16h at 23°C. The solvent was removed in vacuo and the residue purified by solid phase extraction (Isolute SCX sulphonic acid column) eluting with methanol followed by 10% 0.880 ammonia solution in methanol, to give the title compound as a clear gum (0.035g).

LC/MS (system A) Rt 2.34min Mass spectrum *m/z* 493 [MH$^+$].

Example 184: 4-({[({[4-(3,4-Dichlorobenzyl)-1,4-oxazepan-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide

To a solution of 1,1'-carbonyldiimidazole (0.041g) in dichloromethane (2ml) at 0°C was added dropwise a solution of Intermediate 41 (0.079g) in dichloromethane (2ml). The mixture was stirred at 0°C for 1h and at 22°C for 1h, re-cooled to approximately 0°C and a solution of 4-aminomethylbenzamide (0.041g) in a 1:1 mixture of dichloromethane and N,N-dimethylformamide (4ml) was added dropwise. The mixture was stirred at 0°C for 1h and at 22°C for 1h, and applied in two equal portions to ion exchange cartridges (2g Isolute SCX pre-conditioned with methanol). Elution with methanol (3 column volumes) followed 10% 0.880 ammonia in methanol (2 column volumes) and evaporation of the basic fractions in vacuo gave the crude product. Purification by Biotage flash chromatography on a silica gel cartridge (8g), eluting with 150:8:1 dichloromethane/ethanol/0.880 ammonia, gave the title compound as a white solid (0.0186g).

LCMS (system A) R_t 2.22min Mass Spectrum *m/z* 465 [MH^+]

Example 185: 4-[({[({(2S)-4-[1-(3,4-Dichlorophenyl)ethyl]morpholin-2-yl}methyl)amino]carbonyl}amino)methyl]benzamide, isomer II

Intermediate 35 (0.045g) in dichloromethane (1ml) was treated with N,N-diisopropylethylamine (0.021ml) in a 5ml vial (Pierce Reacti-Vial™) followed by 4-aminomethylbenzamide (0.017g). The mixture was sealed under nitrogen and stirred at room temperature for 18h. The solution was then applied to a sulphonic acid ion exchange cartridge (2g Isolute SCX) which had been pre-treated with methanol. The cartridge was eluted with methanol (7 column volumes) followed by 10% 0.880 ammonia in methanol (3 column volumes), and the basic fractions combined and concentrated in vacuo to give a yellow gum. Further purification by chromatography on silica gel (Varian Bond Elut 1g cartridge), eluting with 10% methanol in ethyl acetate, gave the title compound as a yellow gum (0.036g).

LC/MS (System A) R_t 2.25min Mass spectrum *m/z* 465 [MH^+]

Example 186: 4-[({[({(2S)-4-[1-(3,4-Dichlorophenyl)ethyl]morpholin-2-yl}methyl)amino]carbonyl}amino)methyl]benzamide, isomer I

Intermediate 34 (0.045g) in dichloromethane (1ml) was treated with N,N-diisopropylethylamine (0.021ml) in a 5ml vial (Pierce Reacti-Vial™) followed by 4-aminomethylbenzamide (0.017g). The mixture was sealed under nitrogen and stirred at room temperature for 18h. The solution was then applied to a sulphonic acid ion exchange cartridge (2g Isolute SCX) which had been pre-treated with methanol. The cartridge was eluted with methanol (7 column volumes) followed by 10% 0.880 ammonia in methanol (3 column volumes), and the basic fractions combined and concentrated in vacuo to give a yellow gum. Further purification by chromatography on silica gel (Varian Bond Elut 1g cartridge), eluting with 10% methanol in ethyl acetate gave the title compound as a yellow gum (0.036g).

LC/MS (System A) R_t 2.27min. Mass spectrum *m/z* 465 [MH^+].

Example 187: 4-{[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}-N-methylbutanamide

N,N'-carbonyldiimidazole (0.0132g) was added to a stirred solution of Intermediate 26 (0.030g) in N,N-dimethylformamide (2ml), and the mixture stirred at 22°C under nitrogen for 40min. Methylamine (2.0M solution in tetrahydrofuran, 0.102ml) was added, and stirring was continued at 22°C for 17h. The mixture was applied directly to a sulphonic acid ion exchange cartridge (2g Isolute SCX), and eluted with methanol followed by 10% 0.880 ammonia in

methanol to give a gum (0.042g). Purification by chromatography on silica gel (1g Varian Bond Elut cartridge), eluting with chloroform, ether, ethyl acetate, acetone, and methanol, gave a gum (0.025g), which was further purified by mass directed preparative HPLC to give the title compound as a colourless gum (7.2mg).

LC-MS (System A) Rt 2.11min Mass Spectrum *m/z* 417 [MH^+].

Example 188: 3-{[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}-N-methylpropane-1-sulfonamide

Example 188 was prepared in an analogous manner to that of Example 189

LC-MS (System A): Rt 2.20mins Mass Spectrum *m/z* 453 [MH+].

Example 189: N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[3-(pyrrolidin-1-ylsulfonyl)propyl]urea

A solution of Intermediate 28 (0.027g) in N,N-dimethylformamide (1ml) and dichloromethane (2ml) containing N,N-diisopropylethylamine (0.041ml) was added to a stirred solution of Intermediate 13 (0.051g) in dry dichloromethane (2ml) at room temperature under nitrogen, and the mixture was stirred at room temperature for 21h. The mixture was applied directly to a sulphonic acid ion exchange cartridge (2g Isolute SCX) and eluted with methanol (6 column volumes) followed by 10% 880 ammonia in methanol (3 column volumes); evaporation of the methanol/ammonia fractions gave the crude product (0.063g). Purification by chromatography on silica gel (2g Varian Bond Elut cartridge), eluting with chloroform, ether, ethyl acetate, acetone, and methanol, gave the title compound as a gum (0.036g).

LC-MS (System A) Rt 2.41min. Mass Spectrum *m/z* 493 [MH^+].

Biological Data

The compounds of the Examples were tested in the CCR-3 binding and/or eosinophil chemotaxis assays (assays (a) and (b)) and results were obtained as follows:

Example	CCR-3 Binding Assay (pIC50)	CCR-3 Eosinophil Chemotaxis Assay (fpKi)
2		7.31
3	7.16	
4		7.35
5	6.93	
8		6.94
13		6.39
14	6.18	
16	6.13	

18		5.84
19		5.96
21	6.02	
22	6.02	
23	6.08	
25	6.00	
26		5.85
34	5.70	
37	5.42	
38	5.72	
44	4.98	
47	7.18	
48		7.41
52	8.75	
54	7.96	7.8
57		8.01
136	7.8	8.3
149	7.8	7.8

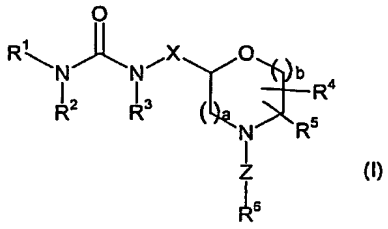
Compounds of Examples 1, 6-7, 9-12, 15, 17, 20, 24, 27-33, 35-36, 39-43, 45-46, 49-51, 53, 55-56, 58-135, 137-148 and 150-189 were also tested in CCR-3 binding assay (assay (a)) and achieved a pIC50 value greater than 5.0.

Example 14 when tested in the ovalbumin sensitised guinea-pig in vivo model (assay (c); 0.2 – 20 mg/kg), showed inhibition of lung eosinophilia and bronchial hyperreactivity.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, aryl-SO_2-Y^1-, C_{1-6} alkyl-G-Y^1-, heteroaryl-G-aryl-Y^1-, J^1-SO_2-Y^1-, $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, $R^{17}NHCO$-Y^1-, $R^{17}NHSO_2$-Y^1-, C_{2-6} alkynyl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which C_{2-6} alkynyl and C_{2-6} alkynyl-Y^1 may be optionally substituted with a $-OR^{17}$ group, which C_{2-6} alkenyl may be optionally substituted by one or more $-COOR^{17}$ groups and which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl optionally substituted by a hydroxy group;

R^3 represents hydrogen or C_{1-6} alkyl;

or R^1 and R^2 may together with the nitrogen atom to which they are attached form a group of formula J^2 wherein said nitrogen atom substitutes for either X^1 or X^2;

t represents 0 or 1.

X represents ethylene or a group of formula CR^eR^f wherein R^e and R^f independently represent hydrogen or C_{1-4} alkyl or R^e and R^f may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R^4 and R^5 independently represent hydrogen or C_{1-4} alkyl;

Z represents a bond, CO, SO_2, $CR^{10}R^7(CH_2)_n$, $(CH_2)_nCR^{10}R^7$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$, $CHR^7(CH_2)_nCO$, $COCHR^7(CH_2)_n$ or $SO_2CHR^7(CH_2)_n$;

R^6 represents C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, aryl-C_{2-6} alkenyl-, -CN or a group of formula $-Y^2$-J^3;

R^7 represents hydrogen, C_{1-4} alkyl, $CONR^8R^9$ or $COOC_{1-6}$ alkyl;

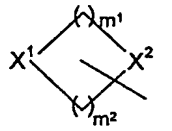
a and b represent 1 or 2, such that a+b represents 2 or 3;

G represents $-SO_2$-, $-SO_2NR^{18}$-, $-NR^{18}SO_2$-, $-NR^{18}CO$-, CO or $-CONR^{18}$-;

n represents an integer from 0 to 4;

M represents a C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl group fused to a monocyclic aryl or monocyclic heteroaryl group;

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{11}, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more -Y^3-aryl, -Y^3-heteroaryl, -Y^3-CO-aryl, -COC_{3-8} cycloalkyl, -Y^3-CO-heteroaryl, -C_{1-6} alkyl, -Y^3-$COOC_{1-6}$ alkyl, -Y^3-COC_{1-6} alkyl, -Y^3-W, -Y^3-CO-W, -Y^3-$NR^{15}R^{16}$, -Y^3-$CONR^{15}R^{16}$, hydroxy, oxo, -Y^3-$SO_2NR^{15}R^{16}$, -Y^3-SO_2C_{1-6} alkyl, -Y^3-SO_2aryl, -Y^3-SO_2heteroaryl, -Y^3-$NR^{13}C_{1-6}$ alkyl, -Y^3-$NR^{13}SO_2C_{1-6}$ alkyl, -Y^3-$NR^{13}CONR^{15}R^{16}$, -Y^3-$NR^{13}COOR^{14}$ or -Y^3-$OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen or C_{1-6} alkyl;

R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or R^{15} and R^{16} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring;

R^{17} and R^{18} independently represent hydrogen or C_{1-6} alkyl;

W represents a saturated or unsaturated, non-aromatic 5-7 membered ring containing between 1 and 3 heteroatoms selected from nitrogen, oxygen or sulphur, optionally substituted with one or more C_{1-6} alkyl, halogen or hydroxy groups;

Y^1, Y^2 and Y^3 independently represent a bond or a group of formula $-(CH_2)_pCR^cR^d(CH_2)_q-$ wherein R^c and R^d independently represent hydrogen or C_{1-4} alkyl or R^c and R^d may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group, and p and q independently represent an integer from 0 to 5 wherein p + q is an integer from 0 to 5;

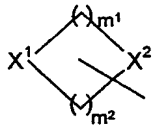
and salts and solvates thereof.

2. A compound of formula (I) according to claim 1 wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, aryl-SO_2-Y^1-, C_{1-6} alkyl-G-Y^1-, J^1-SO_2-

Y^1-, $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, C_{2-6} alkynyl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which C_{2-6} alkynyl and C_{2-6} alkynyl-Y^1 may be optionally substituted with a $-OR^{17}$ group and which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl; and

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

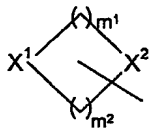
wherein X^1 represents oxygen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{11}, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more -Y^3-aryl, -Y^3-heteroaryl, -Y^3-CO-aryl, -Y^3-CO-heteroaryl, -C_{1-6} alkyl, -Y^3-$COOC_{1-6}$ alkyl, -Y^3-COC_{1-6} alkyl, -Y^3-W, -Y^3-CO-W, -Y^3-$NR^{15}R^{16}$, -Y^3-$CONR^{15}R^{16}$, hydroxy, oxo, -Y^3-$SO_2NR^{15}R^{16}$, -Y^3-SO_2C_{1-6} alkyl, -Y^3-SO_2aryl, -Y^3-SO_2heteroaryl, -Y^3-$NR^{13}C_{1-6}$ alkyl, -Y^3-$NR^{13}SO_2C_{1-6}$ alkyl, -Y^3-$NR^{13}CONR^{15}R^{16}$, -Y^3-$NR^{13}COOR^{14}$ or -Y^3-$OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

3. A compound of formula (I) according to claim 1 wherein R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, -Y^1-J^1, -Y^1-CO-J^1 or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl;

Z represents a bond, CO, $CR^{10}R^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$, $CHR^7(CH_2)_nCO$; and

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, nitrogen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, nitrogen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3, m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when X^2 represents oxygen, nitrogen, NR^{12} or sulphur, m^1and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{15}R^{16}$, $-Y^3-CONR^{15}R^{16}$, hydroxy, oxo, $-Y^3-SO_2NR^{15}R^{16}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{13}C_{1-6}$ alkyl, $-Y^3-NR^{13}SO_2C_{1-6}$ alkyl, $-Y^3-NR^{13}CONR^{15}R^{16}$, $-Y^3-NR^{13}COOR^{14}$ or $-Y^3-OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

4. A compound of formula (I) according to any one of claims 1 to 3 wherein R^1 represents aryl-Y^1- or heteroaryl-Y^1-.

5. A compound of formula (I) according to claim 4 wherein R^1 represents optionally substituted phenyl-Y^1- or tetrazolyl-Y^1- which phenyl and tetrazolyl may be optionally substituted.

6. A compound of formula (I) according to any one of claims 1 to 5 wherein Y^1 represents $-CH_2-$.

7. A compound of formula (I) according to claim 1 wherein X represents methylene.

8. A compound of formula (I) according to claim 1 wherein a and b both represent 1.

9. A compound of formula (I) according to claim 1 or claim 3 wherein Z represents CO, $CHR^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$ or $CHR^7(CH_2)_nCO$.

10. A compound of formula (I) according to claim 9 wherein Z represents CH_2.

11. A compound of formula (I) according to claim 1 wherein R^6 represents phenyl optionally substituted with one or more halogen atoms.

12. A compound of formula (I) according to claim 11 wherein R^6 represents 3,4-dichlorophenyl.

13. A compound of formula (I) according to any one of claims 1 to 12 as described in Examples 1 to 189 or a salt or solvate of any one thereof.

14. A compound of formula (I) according to claim 13 which is 4-({[({[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide or a salt or solvate thereof.

15. A compound of formula (I) according to claim 13 which is N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-2H-tetraazol-5-yl)methyl]urea or a salt or solvate thereof.

16. A compound of formula (I) according to claim 13 which is 4-({[({[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)-N-methylbenzamide or a salt or solvate thereof.

17. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 16 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

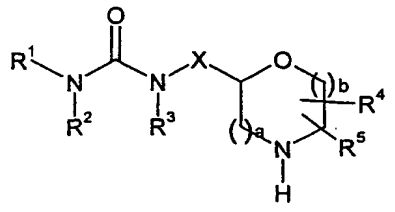
18. A compound of formula (I) as defined in any one of claims 1 to 16 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

19. Use of a compound of formula (I) as defined in any one of claims 1 to 16 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of inflammatory diseases.

20. A method of treatment or prophylaxis of inflammatory diseases eg. asthma which comprises administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 16 or a pharmaceutically acceptable salt or solvate thereof.

21. A process for preparing a compound of formula (I) as defined in any one of claims 1 to 16 which comprises:

(a) reacting a compound of formula (II)

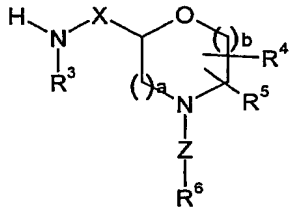


(II)

wherein R^1, R^2, R^3, R^4, R^5, X, a and b are as defined in claim 1, or a protected derivative thereof, with a compound of formula

L^1-Z-R^6, wherein Z and R^6 are as defined in claim 1 and L^1 represents a suitable leaving group; or

(b) forming a compound of formula (I) wherein R^2 represents hydrogen which comprises reacting a compound of formula (III)

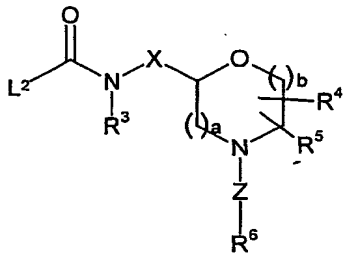


(III)

wherein R^3, R^4, R^5, R^6, Z, X, a and b are as defined in claim 1, or a protected derivative thereof, with a compound of formula

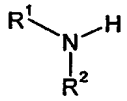
R^1-N=C=O, wherein R^1 is as defined in claim 1; or

(c) reacting a compound of formula (IV)



(IV)

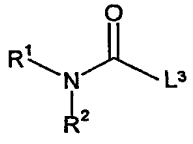
wherein R^3, R^4, R^5, R^6, Z, X, a and b are as defined in claim 1 and L^2 represents a suitable leaving group, or a protected derivative thereof, with a compound of formula (V)



(V)

wherein R^1 and R^2 are as defined in claim 1 or a protected derivative thereof; or

(d) reacting a compound of formula (VI)



(VI)

wherein R^1 and R^2 are as defined in claim 1 and L^3 represents a suitable leaving group, or a protected derivative thereof, with a compound of formula (III), or a protected derivative thereof; or

(e) deprotecting a compound of formula (I) which is protected; or

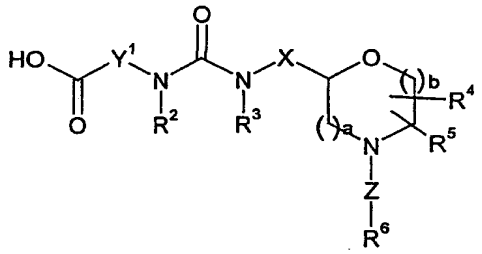
(f) interconversion of other compounds of formula (I).

22. A process for preparing a compound of formula (I) as defined in any one of claims 1 to 16 which comprises:

(g) forming a compound of formula (I) wherein R^1 and R^2 together with the nitrogen atom to which they are attached form a group of formula J^2 wherein said nitrogen atom substitutes for either X^1 or X^2 which comprises reacting a compound of formula (IV) or a protected derivative thereof with a compound of formula J^2H, provided that the compound of formula J^2H has a free –NH group; or

(h) forming a compound of formula (I) wherein Z represents $CR^{10}R^7(CH_2)_n$, wherein R^{10} represents hydrogen, which comprises reacting a compound of formula (II) or a protected derivative thereof with a compound of formula $R^7CO(CH_2)_nR^6$, followed by reduction of the resultant imine; or

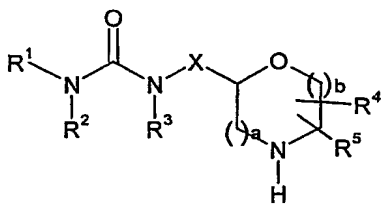
(i) forming a compound of formula (I) wherein R^1 represents C_{1-6} alkyl-G-Y^1-, wherein G represents $-NR^{18}CO-$, which comprises reacting a compound of formula (VII)



(VII)

or a protected derivative thereof wherein R^2, R^3, R^4, R^5, R^6, Y^1 X, Z, a and b are as defined in claim 1, with a compound of formula C_{1-6} alkyl-NHR^{18}.

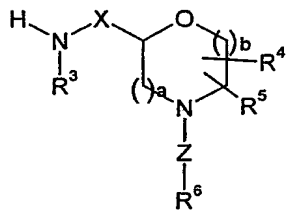
23. A compound of formula (II)



(II)

wherein R^1, R^2, R^3, R^4, R^5, X, a and b are as defined in claim 1, or a protected derivative thereof, or a salt or solvate thereof.

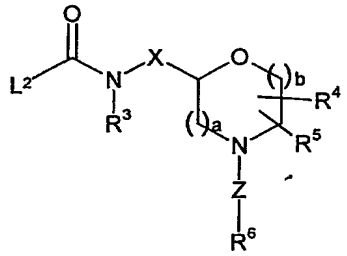
24. A compound of formula (III)



(III)

wherein R^3, R^4, R^5, R^6, Z, X, a and b are as defined in claim 1, or a protected derivative thereof, or a salt or solvate thereof.

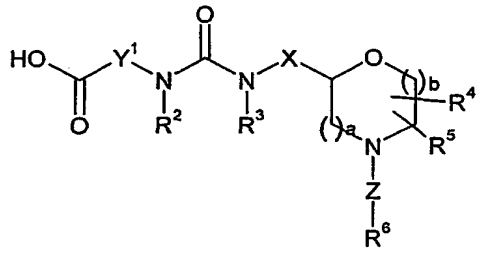
25. A compound of formula (IV)



(IV)

wherein R^3, R^4, R^5, R^6, Z, X, a and b are as defined in claim 1 and L^2 represents a suitable leaving group, or a protected derivative thereof, or a salt or solvate thereof.

26. A compound of formula (VII)



(VII)

wherein R^2, R^3, R^4, R^5, R^6, Y^1 X, Z, a and b are as defined in claim 1, or a protected derivative thereof, or a salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/04350

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D265/30 C07D267/10 A61K31/5375 A61K31/553 A61P11/06
C07D413/06 C07D413/12 C07D417/12 C07D471/04 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 31032 A (HOFFMANN LA ROCHE) 2 June 2000 (2000-06-02) cited in the application claims 1,22,32; example 11	1-24,26
Y	WO 00 35876 A (DU PONT PHARM CO) 22 June 2000 (2000-06-22) cited in the application page 68, line 10 - line 24; claims 1,44,48,50	1-24,26
Y	WO 00 35449 A (DU PONT PHARM CO) 22 June 2000 (2000-06-22) cited in the application page 67, line 13 - line 28; claims 1,11,23,24	1-24,26

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2001	11/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 01/04350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 760 362 A (NISSHIN FLOUR MILLING CO) 5 March 1997 (1997-03-05) cited in the application page 5, line 48 -page 7, line 18; claims 1,5; examples 21,22	1-21,24
X	PATENT ABSTRACTS OF JAPAN vol. 016, no. 544 (C-1004), 13 November 1992 (1992-11-13) -& JP 04 208267 A (MITSUI PETROCHEM IND LTD;OTHERS: 01), 29 July 1992 (1992-07-29) cited in the application compounds 1073 and (1) abstract	1-21,24
X	HARADA H ET AL: "DEVELOPMENT OF POTENT SEROTONIN-3 (5-HT3) RECEPTOR ANTAGONISTS. I. STRUCTURE-ACTIVITY RELATIONSHIPS OF 2-ALKOXY-4-AMINO-5-CLOROBENZAMIDE DERIVATIVES" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 43, no. 8, 1995, pages 1364-1378, XP002077996 ISSN: 0009-2363 chart 1; table 3	24
X	KATO S ET AL: "NOVEL BENZAMIDES AS SELECTIVE AND POTENT GASTROKINETIC AGENTS III. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 4-AMINO-5-CHLORO-2-METHOXY- AND 2-ETHOXY-N-(4-SUBSTITUTED 2-MORPHOLINYL)METHYL-BENZAMIDES" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 40, no. 3, March 1992 (1992-03), pages 652-660, XP001037843 ISSN: 0009-2363 compounds 6 and 10; table 1	24

-/--

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 01/04350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KATO S ET AL: "NOVEL BENZAMIDES AS SELECTIVE AND POTENT GASTROKINETIC AGENTS 2. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 4-AMINO-5-CHLORO-2-ETHOXY-N-4-(4-FLUOROBEN ZYL)-2-MORPHOLINYL METHYLBENZAMIDE CITRATE (AS-4370) AND RELATED COMPOUNDS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 2, February 1991 (1991-02), pages 616-624, XP001037842 ISSN: 0022-2623 compound 5; table I	24
X	KATO S ET AL: "NOVEL BENZAMIDES AS SELECTIVE AND POTENT GASTRIC PROKINETIC AGENTS 1. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF N-(2-MORPHOLINYL)ALKYLBENZAMIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 33, no. 5, May 1990 (1990-05), pages 1406-1413, XP001037844 ISSN: 0022-2623 compounds 7 and 11	24

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 23,24,26 searched partially; 25 not searched

Present claims 23-26 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The term "protected derivative thereof" does not enable the skilled person to determine which specific compounds fall within the scope of said definition. Consequently, the search does not include "protected derivatives" of the claimed compounds.

The same applies to the term "suitable leaving group" used in claim 25. In this case, the lack of clarity renders a meaningful search of said claim impossible.

Moreover, the initial phase of the search for claim 24 revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which part of said claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of claim 24 is impossible. Consequently, only a selection of novelty destroying documents are cited.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/GB 01/04350

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0031032	A	02-06-2000	AU	1382500 A	13-06-2000
			BR	9915520 A	17-07-2001
			DE	19955794 A1	31-05-2000
			WO	0031032 A1	02-06-2000
			EP	1131288 A1	12-09-2001
			ES	2158814 A1	01-09-2001
			FR	2786185 A1	26-05-2000
			GB	2343893 A	24-05-2000
			NO	20012411 A	16-05-2001
			US	6166015 A	26-12-2000
WO 0035876	A	22-06-2000	AU	2056700 A	03-07-2000
			EP	1140833 A1	10-10-2001
			WO	0035876 A1	22-06-2000
WO 0035449	A	22-06-2000	AU	1940600 A	03-07-2000
			AU	2057200 A	03-07-2000
			AU	2482100 A	03-07-2000
			AU	3126600 A	03-07-2000
			AU	3126700 A	03-07-2000
			EP	1161240 A1	12-12-2001
			EP	1140086 A1	10-10-2001
			EP	1158980 A1	05-12-2001
			EP	1140087 A1	10-10-2001
			EP	1156807 A1	28-11-2001
			NO	20012977 A	20-08-2001
			WO	0035449 A1	22-06-2000
			WO	0035451 A1	22-06-2000
			WO	0035452 A1	22-06-2000
			WO	0035453 A1	22-06-2000
			WO	0035454 A1	22-06-2000
			AU	3634001 A	08-05-2001
			WO	0130752 A2	03-05-2001
EP 0760362	A	05-03-1997	BR	9507892 A	18-11-1997
			CA	2189964 A1	23-11-1995
			EP	0760362 A1	05-03-1997
			WO	9531431 A1	23-11-1995
			US	5753654 A	19-05-1998
JP 04208267	A	29-07-1992	JP	3087763 B2	11-09-2000